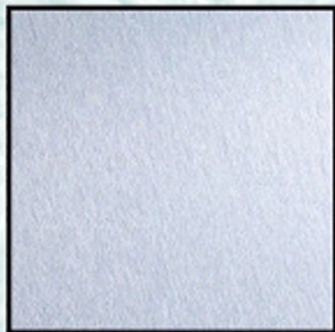




ELSEVIER INSIGHTS



BIOSCIENCE AND BIOENGINEERING OF TITANIUM MATERIALS

SECOND EDITION

YOSHIKI OSHIDA

VISIT...

LANZAROTE
Caliente.COM

Bioscience and Bioengineering of Titanium Materials

This page intentionally left blank

Bioscience and Bioengineering of Titanium Materials

Second Edition

Yoshiki Oshida, MS, PhD

*Professor Emeritus,
School of Dentistry,
Indiana University, IUPUI,
Indianapolis, IN, USA*

*Adjunct Professor,
School of Dentistry,
University of California San Francisco,
San Francisco, CA, USA*



AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Elsevier
32 Jamestown Road, London NW1 7BY
225 Wyman Street, Waltham, MA 02451, USA

Second edition

Copyright © 2013, 2007 Elsevier B.V. All rights reserved

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangement with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

ISBN: 978-0-444-62625-7

For information on all Elsevier publications
visit our website at store.elsevier.com

This book has been manufactured using Print On Demand technology. Each copy is produced to order and is limited to black ink. The online version of this book will show color figures where appropriate.

Working together to grow
libraries in developing countries

www.elsevier.com | www.bookaid.org | www.sabre.org

ELSEVIER

BOOK AID
International

Sabre Foundation

Dedicated

*To my wife
for putting up with me*

&

*To my parents
for their love, support, and encouragement*

This page intentionally left blank

Contents

Prologue	xiii
Preface for the Second Edition	xv
1 Introduction	1
References	6
2 Materials Classification	9
2.1 Introduction	9
2.2 General Classification	10
2.3 Medical/Dental Titanium Materials	15
2.3.1 Commercially Pure Titanium	15
2.3.2 Ti–6Al–4V	16
2.3.3 Ti–6Al–7Nb	17
2.3.4 Ti–3Al–2.5V	17
2.3.5 Ti–5Al–3Mo–4Zr	17
2.3.6 Ti–5Al–2.5Fe	17
2.3.7 Ti–5Al–2Mo–2Fe (SP700)	18
2.3.8 Ti–Ni	18
2.3.9 Ni-Free Ti-Based Alloys, and Ti–Nb Alloys	21
2.3.10 Ti–Cu	22
2.3.11 Ti–Mo	23
2.3.12 Ti–Al Alloys	24
2.3.13 Other Ti-Based Alloys	25
References	28
3 Chemical and Electrochemical Reactions	35
3.1 Introduction	35
3.2 Discoloration	36
3.3 Corrosion in Media Containing Fluorine Ion and Bleaching Agents	38
3.4 Corrosion under Influences of Environmental and Mechanical Actions	42
3.5 Metal Ion Release and Dissolution	52
3.6 Galvanic Corrosion	61
3.7 Microbiology-Induced Corrosion	63
3.8 Reaction with Hydrogen	70
References	73

4	Oxidation and Oxides	87
4.1	Introduction	87
4.2	Formation of Titanium Oxides	88
4.2.1	Air-Formed Oxide	89
4.2.2	Passivation	90
4.2.3	Oxidation at Elevated Temperatures	92
4.3	Influences on Biological Processes	94
4.4	Crystal Structures of Titanium Oxides	95
4.5	Characterization of Oxides	98
4.6	Unique Applications of Titanium Oxide	99
4.7	Oxide Growth, Stability, and Breakdown	99
4.8	Reaction with Hydrogen Peroxide	102
4.9	Applications of Advanced Technologies	104
4.9.1	Nanotube Fabrication	104
4.9.2	Hybrid Oxides Formation	105
4.9.3	Nano Titania Film Formation	106
4.9.4	UV Treatment	106
	References	107
5	Mechanical and Tribological Behaviors	117
5.1	Introduction	117
5.2	Fatigue	117
5.3	Fretting	121
5.4	Fracture and Fracture Toughness	122
5.5	Biotribological Actions	124
5.5.1	In General	124
5.5.2	Friction	125
5.5.3	Wear and Wear Debris Toxicity	127
5.6	Improvement for Antitribological Deterioration	131
	References	132
6	Biological Reactions	139
6.1	Introduction	139
6.2	Toxicity	139
6.3	Cytocompatibility (Toxicity to Cells)	142
6.4	Allergic Reaction	146
6.5	Metabolism	149
6.6	Biocompatibility	150
6.7	Biomechanical Compatibility	156
	References	161
7	Implant-Related Biological Reactions	169
7.1	Introduction	169
7.2	Bone Healing	172
7.3	Bone Grafting	174
7.4	Hemocompatibility	175

7.5	Cell Adhesion, Adsorption, Spreading, and Proliferation	177
7.6	Roughness and Cellular Response to Biomaterials	190
7.7	Cell Growth	193
7.8	Tissue Reaction and Bone Ingrowth	195
7.9	Osteointegration and Bone—Implant Interface	203
7.10	Some Adverse Factors for Loosening Implants	209
7.11	Nonmetallic Implants	210
	References	210
8	Implant Application	225
8.1	Introduction	225
8.2	Intraoral Implants Versus Extraoral Implants	229
8.3	Clinical Reports	230
8.4	Surface and Interface Characterizations	237
8.5	Reactions in Chemical and Mechanical Environments	242
8.6	Reaction in Biological Environment	248
8.7	Surface Modification Effects	258
	References	260
9	Other Applications	269
9.1	Introduction	269
9.2	Denture Bases	269
9.3	Crowns and Bridges, and Abutment	271
9.4	Clasps	281
9.5	Posts and Cores	281
9.6	Titanium Fiber and Oxide Powder as Reinforcement for Bone Cement	283
9.7	Sealer Material	283
9.8	Shape Memory Effect Dental Implant	284
9.9	Orthodontic Appliances	284
9.10	Endodontic Files and Reamers	287
9.11	Clamps and Staples	290
9.12	Stents	290
9.13	MRI Safety and Image Compatibility	293
	References	294
10	Fabrication Technologies	303
10.1	Introduction	303
10.2	Casting	303
10.3	Machining	307
10.4	Electro-discharge Machining	308
10.5	CAD/CAM	309
10.6	Isothermal Forging	310
10.7	Superplastic Forming	310
10.8	DB and SPF/DB	313
10.9	Powder Metallurgy	314

10.10	Metal Injection Molding	317
10.11	Mechanical Alloying	318
10.12	Laser Processing	318
10.12.1	Welding	319
10.12.2	Forming	322
10.12.3	Machining	323
10.12.4	Surface Treatments	324
10.13	Friction Stir Welding	326
10.14	Soldering	327
10.15	Heat Treatment	327
10.16	Coating	328
10.17	Electrospinning	329
10.18	Electron Beam Melting	330
10.19	Additive Manufacturing	331
	References	332
11	Surface Modifications	341
11.1	Introduction	341
11.2	Mechanical Modification	343
11.2.1	Sandblasting and Surface Texturing	343
11.2.2	Shot-Peening and Laser-Peening	352
11.3	Chemical, Electrochemical, Thermal, and Physical Modifications	353
11.3.1	Chemical and Electrochemical Treatment	354
11.3.2	Chemical + Thermal	361
11.3.3	Alkali + Thermal	363
11.3.4	Thermal and Physical	363
11.3.5	UV Treatment	365
11.4	Coating	367
11.4.1	Carbon, Glass, and Ceramics Coating	368
11.4.2	HA Coating	370
11.4.3	Ca-P and TCP Coating	391
11.4.4	Composite Coating	399
11.4.5	TiN and TiC Coating	403
11.4.6	Ti Coating	409
11.4.7	TiO ₂ Film and Coating	413
11.4.8	Other Coatings	418
11.5	Collagen, Protein, and CHI Coating	420
11.5.1	Collagen Coating	427
11.5.2	Protein Coating	431
11.5.3	Peptide Coating	432
11.5.4	CHI Coating	433
11.6	Coloring	435
	References	436

12	Advanced Materials, Technologies, and Processes	457
12.1	Introduction	457
12.2	Materials, Structures, and Processes	459
12.3	Functionally Graded Materials and Design Concept	461
12.4	Controlled Porosity/Foamed Structures	464
12.4.1	Controlled Porosity	464
12.4.2	Porosity-Controlled Surface and Texturing	466
12.4.3	Mechanical Property and Its Effect	468
12.4.4	Foam Metal	469
12.5	Near-Net Shape Forming	471
12.5.1	Net Shape Forming	471
12.5.2	Net Shape Nanostructured	472
12.5.3	Near-Net Shape Technology	472
12.6	Nanotechnology—Materials and Structures	474
12.6.1	Nanostructured Hydroxyapatite	475
12.6.2	Nanostructured Titanium	476
12.6.3	Nanostructured Titania	478
12.6.4	Tissue Engineering	480
12.7	Hybridization and Multifunctionality	483
12.8	Bioengineering and Biomaterial-Integrated Implant System	486
	References	490
	Epilogue	499

This page intentionally left blank

Prologue

Writing a book based on reviewing published articles like this book is a typical example of evidence-based learning—EBL. The evidence-based literature review can provide foundation skills in research-oriented bibliographic inquiry, with an emphasis on such review and synthesis of applicable literature. All information is obtained from numerous sources provided by scholars and researchers who are involved in various disciplines. Available sources possess a variety of features, especially the degree of reliability. There is a known rank of reliability for evidence sources, which is particularly important in medicine and dental fields (from the most to least reliable evidence source): (1) clinical reports using placebo and double blind studies, (2) clinical reports not using placebos, but conducted according to well-prepared statistical test plans, (3) study reports on time effect on one group of patients, (4) study reports, at one limited time, on many groups of patients, (5) case reports on a new technique and/or idea, and (6) retrospective reports on clinical evidence. Unfortunately, the number of published articles increases in this descending reliability order.

The most remarkable advantage of the EBL-type reviewing of numerous published articles is to encounter an unexpected idea and issue that might provide a fundamental basis persisting in all related but separately and scattered manner being presented in different sources. Accordingly, it is actually an inductive practice.

Comparing articles seen in medical/dental journals and those published in engineering journals, one can see a big difference between them. Obtained results present in the medical/dental journals are normally further analyzed statistically, while the data presented in the engineering journals are normally not subjected to statistical analysis; rather, characterization of data is considered more important to interpret results. Even though a statistical analysis is conducted for medical/dental results, there are some cases which do not reach a conclusive point. For example, although the mercury issue (which is used for condensation of dental amalgam alloy to form Ag_2Hg_3 and Sn_{7-8}Hg) has been debated for more than 20 years, we still have not come to one solid consensus on its safety as yet. In fact, mercury amalgam has been completely abandoned in Scandinavian countries and Japan, whereas it is still used in the United States and other countries, although tooth-color restorations are becoming more popular from aesthetic reasons.

There is another challenge in the medical and dental field, namely the controversial relationship between *in vivo* test results and those obtained by *in vitro* tests. To make this situation more complicated and confusing, there could be differences even among various *in vivo* tests, due to different models (different types of animals versus humans). Moreover, it is almost impossible to comply and summarize

to extract any conclusiveness from various *in vitro* test results, since it is very rare to find articles where identical test methods were employed, unless some standardized (specified) methodology was followed. For example, it is easy to list at least 10 electrolytes for electrochemical evaluation of the corrosion behavior and resistance of a dental metallic material. In addition to this, wide variations in pH value, concentration, temperature, and other intraoral environmental factors can easily alter the experimental outcomes. This is the reason why in the materials science and engineering area phenomenon is most importantly characterized to find the basic mechanisms as well as kinetics. Once the basics are elucidated, if any environmental factor is changed, the possible results would not be hard to anticipate. Although a statistical test on obtained data is considered a powerful tool to analyze results, it should be based on postulated assumptions (which should be statistically tested once data are collected), and the results are not applicable to entire patient populations. Suppose a newly developed medicine was statistically evaluated, and *in vivo* test results showed that it is effective to 95% of the patient population; this indicates, on the other side of the coin, that it definitely does not work for the remaining 5% of human patients.

In this book, such differentiation and comparison in analyzing results between medical/dental and engineering fields will be emphasized and an attempt has been made to fill the gaps if possible. The materials and most of the technologies employed in the medical and dental fields were originally developed in the engineering/technology field. If they prove their safety and can be miniaturized, they can be accommodated for human uses. Such successfully performed technology transfers from engineering techniques to medical/dental applications are also introduced in this book. Hence, this book has a two-fold uniqueness: (1) the EBL concept has been applied and practiced throughout the entire course of preparing, writing, and editing this book and (2) a bridging of the gap between the medical/dental fields and engineering/technology areas, owing to the author's unique experience of 20 years each in both fields.

Preface for the Second Edition

Since the first edition of this book (more accurately, since June 2006 when I stopped to read articles for preparing the book, as I mentioned in the Epilogue in the first edition), there are certain areas where technologies and their associated materials have been remarkably advanced and developed. It is obvious that no course in science and engineering may remain static. The major modifications to this edition have been made through paying attention to the ever-advancing technology and materials development in dental/medical applications of titanium materials, particularly in the area of tissue engineering and the field of surface modification. For example, in the area of surface modifications for both intra- and extraoral implants, nanotechnology has been fully employed to promote the early stage of osteointegration (through a bioactive connection between the placed implant and the receiving bone structure); this is because placed extraoral implants are no longer cement retained due to potential problems such as cement disease. This nanotechnology should include nanosize tube formation, nanosize powder coatings, and nanosized texturing. Hybridization is another technique to be mentioned, including hybridization of different sizes of the same types of materials and hybridization of more than two different types of materials. Surface modification is also extensively achieved at relatively lower temperature to avoid unwanted metallurgical damage of the titanium material substrates. Graded functioning (GF) design concepts for structure as well as material development have also been successfully utilized to fabricate the surface zone of the implants more effectively and efficiently, so that both morphological and mechanical compatibilities between placed implants and receiving hard tissues can be easily attained. Accordingly, in this second edition, every chapter has been revised extensively, reflecting developments during the past 6 years. Some information described in Chapter 12 in the first edition has been moved to the appropriate sections in Chapters 10, 11, and 12 in this second edition. Some materials that were listed as future titanium materials needed to be listed in Chapter 2 as ordinarily used materials (like CpTi and Ti-6Al-4V, and many others). New activities on generating bioactive titanium surfaces are reviewed in Chapter 12. Since the first edition (2007), three new journals related to biomaterials and bioengineering have been launched. Altogether, approximately 500 updated references have been added to this revised edition. Although substantial expansions were made in this edition, a bridging between engineering and the dental/medical field should remain unchanged as a backbone of this book.

This page intentionally left blank

1 Introduction

In Greek mythology, the giant god Titan, who was the son of Uranos (Father Heaven) and Gaia (Mother Earth), had lost several wars against the gods of Olympus, which resulted in his being confined in the underworld. The element *Titanium* was discovered by German chemist Martin Heinrich Klaproth, who confirmed it as a new element; in 1795, he named it for the Latin word for Earth (also the name for the Titans of Greek myth).¹

Because of the unique properties of titanium materials, including their lightweight and high specific strength (which is also referred to as high strength-to-weight ratio), low modulus of elasticity, and excellent corrosion resistance, they (both unalloyed and alloyed) have been important materials for the aerospace industry since the early 1950s [1]. It was hard to predict, at that time, that titanium materials would have such importance not only for industrial/engineering applications but also for dental and medical applications.

Nowadays, the medical device industry increasingly relies on knowledge of materials science and engineering to develop sophisticated replacements for natural tissues. For example, the \$3.2 billion cardiac stent market has expanded over the past decade (2000 through 2010) due to the development of flexible polymer balloon catheters that expand obstructed blood vessels; metallic wire meshes that provide structural support to blood vessels; and biodegradable polymers that release antiproliferative pharmacologic agents in order to minimize closure (restenosis) of blood vessels [2]. Estimates of the numbers of biomedical devices in the US incorporating biomaterials in 2002 include 448,000 for total hip joint replacements, 452,000 for knee joint replacements, 24,000 for shoulder joint replacements, 854,000 for dental implants, 1,204,000 for coronary stents, and 1,328,000 for coronary catheters [3,4]. Novel biomaterials, including biologically derived materials and nanoscale materials, are being developed for advanced prostheses and functional medical devices. These biomaterials will provide integration of multiple functions, miniaturization of devices, an increase in stability, and a decrease in cost. It is anticipated that novel medical devices and prostheses will play a significant role in improving the quality of health care for patients [2]. However, the difficulty of precisely determining biomaterial behavior during longer periods of time

¹ <http://www.scescye.net/~woods/elements/titanium;> <http://en.wikipedia.org/wiki/Titanium>

and under different human-related environments makes it necessary to investigate implant materials, taking into account the influence of the large number of system parameters. The complex nature and numerous applications of biomaterials require knowledge about different variables in regard to biocompatibility, corrosion behavior, mechanical characteristics, stability and durability in aggressive environments including wear and friction activities [3].

The choice of materials used for designing a medical implant is governed by biocompatibility, bioadhesion, biofunctionality, corrosion resistance, etc. Understanding liquid–solid interactions through the behavior of the liquid–solid interface is very important in biomedical implants [5]. Liquid–solid interaction may or may not include chemical reactions, and the degree of liquid spreading over the solid surface (wetting) may vary based on the chemical properties of the materials involved (surface free energy) and the topography of the solid surface (roughness). The wetting of solid surfaces by biological fluids is often necessary for a chain of biological events to unfurl (expand) so that a foreign material may be accepted *in vivo* and thus become bioactive [5].

The integration of biology into materials science and engineering can be complicated by the lack of a common framework and common language among otherwise disparate disciplines. The integration of metallurgy, ceramics, and polymers into materials science and engineering is based upon processing–structure–property relationships that are now well accepted. The author has taught “Materials and Processes in Manufacturing” (MFE636) at the Syracuse University College of Engineering Graduate School (Syracuse NY, USA) for years, and a whole course scenario and class presentation has been prepared based on the processing–structure–property concept. Therefore, a common paradigm might also help unify the vast array of perspectives and challenges present in the interdisciplinary study of biomaterials, biological materials, and biomimetic materials. The traditional Materials Science and Engineering paradigm was modified to account for the adaptive and hierarchical nature of biological materials [6].

Research and development in materials design, manufacturing technologies, characterization, and evaluation methods involved in titanium materials are some of the best examples of interdisciplinary science and technology; such disciplines might include physics, chemistry, metallurgy, mechanics, and surface and interface sciences, as well as biological science, engineering, and technology (see Figure 12.1). One of the typical examples can be seen in dental and orthopedic implant systems, which have been developed by integrating industrial engineering, bioengineering, and supportive advanced techniques.

Although empiricism and trial and error played a major role in the early stage of research and development on titanium materials, in the last 30 years progress has been made toward a multidisciplinary scientific approach to the study of titanium materials and the development of materials with better performance and properties [7]. The research and development of titanium materials has been heavily dependent on the aerospace industries, and this area will continue to be a significant percentage of total consumption of titanium materials in the coming years [8]. Titanium usage on Boeing aircraft has continuously increased from 1% on the 727

(1963) to 3% on the 747 (1969), 5% on the 757 (1983), and 9% on the 777 (1994). Over the last decade, the focus of titanium alloy development has shifted from aerospace [9] to industrial applications [8]. Different industrial sectors have been looking for different types of development in new titanium alloys. They include Ti-5.8Al-4Sn-3.5Zr-0.7Nb-0.5Mo-0.35Si-0.06C, Ti-6Al-2Sn-4Zr-6Mo, and Ti-4Al-4Mo-2Sn-0.5Si for gas turbine engine materials; Ti-10V-2Fe-3Al, Ti-15V-3Cr-3Sn-3Al, and Ti-15Mo-2.8Al-3Nb-0.2Si for airframe materials; Ti-6Al-1.8Fe-0.2Si for ballistic armor; Ti-6.8Mo-4.5Fe-1.5Al for geothermal and offshore tubular materials; Ti-15V-3Cr-3Sn-3Al (having higher strength and lower modulus) for sporting goods [10]; V-free Ti-6Al-4V equivalent alloys for medical and dental applications; and NiTi—Cu alloys for medical orthopedic devices.

Not only materials but also the technologies developed and successfully used in industry can be transferred to medical and dental areas. The computer-aided design and machining (CAD/CAM) process is an excellent example of a technology currently used to design and fabricate dental restorations. Investigators are also combining CAD and artificial intelligence (AI) to design complex prosthetic devices such as partial dentures. Computers have also been used to analyze the stress levels and stress distribution on dental restorations, dental implants, and orthopedic implants. They can simulate internal stress distributions under different conditions and loading situations, and the results can be used to optimize the CAD process (e.g., two- or three-dimensional finite element modeling and stress analyses). The application of lasers to dentistry is another good example of technology transfer [11]. Various methods of laser application for surface modifications of metals have also been introduced, and include cutting, welding, surface hardening, laser surface alloying, and forming [12]. Superplastic forming (SPF) of denture bases, and superplastic forming with diffusion bonding (SPF/DB) for modification and roughening of implant surfaces, are other excellent examples of the technical transfer. These transferred technologies are not necessary to be limited to technology itself, but they can also include technical concepts such as composites, as well as gradually functional structures, which can be frequently seen in the surface modification of implant systems to promote bone ingrowth.

The popularity of titanium and its alloys in dental and medical fields can be recognized by counting the manuscripts published in different journals, most of which will be cited in this review. Referring to Figure 1.1, there are three straight lines in semilog plot for demonstrating the total accumulated number of published articles for every 5 years. The first top line represents accumulated numbers of all articles listed in Chemical Abstract. Therefore, the counted articles are scattered in wider areas such as refining, metallurgy, medicine, dentistry, bioengineering, engineering, industries, pure chemistry, and chemical engineering. The second straight line is obtained when the search area is limited to materials and science in both the engineering and medical/dentistry fields. If our search is defined within only medicine/dentistry, we still have an exponential increase in publications. From the third straight line, only eight papers (not shown in the figure) were published in the time period from 1960 to 1965, followed by 156 papers in 1966–1970, 352 in 1971–1975, 309 in 1976–1980, 493 in 1981–1985, 916 in 1986–1990; the

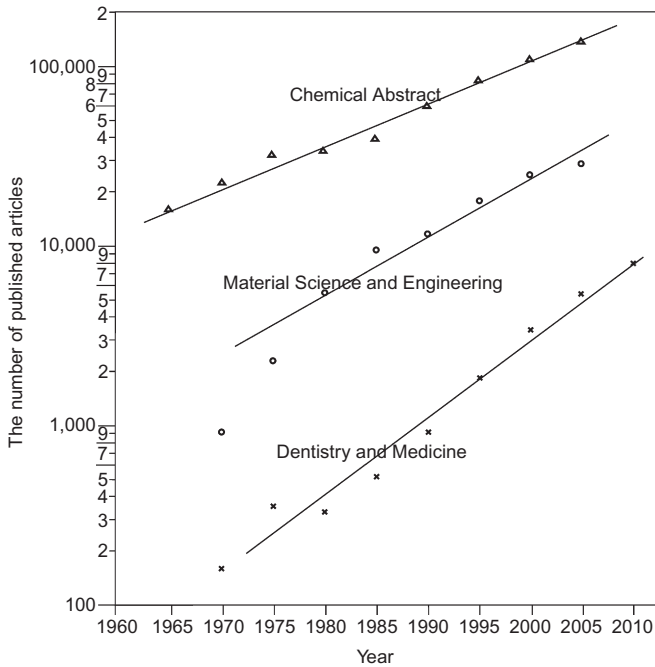


Figure 1.1 Accumulated number of published articles on titanium materials for every 5 years.

figure jumped to 1914 papers in the 5-year period from 1991 to 1995. In 1996–2000, we had already reached more than 3000 articles, followed by 5500 articles published during a 5-year period from 2001 to 2005. Since the first edition of this book in 2007, there have been about 8000 articles published, related to dentistry and medicine.

The reason for the ever-increasing number of publications on Titanium Biomaterials even during the last 5 years (2005–2010) is partially due to the fact that three major international journals in biomaterials, bioengineering, and biomechanics have been successfully launched. The exponentially increasing trend of published papers on medical and dental titanium materials may be attributed to different reasons that might include (i) needs from medical and dental sectors, (ii) increased numbers of researchers and scientists involved in these medical titanium materials, and (iii) an expanded industrial scale associated with the above.

Now, 15 years later from the previous forecasting (in 1996) on titanium industry and materials developments [8–10], another remarkable change has been seen. In addition to the ever-growing aerospace applications, precise forming technologies have been developed such as near-net shape (NNS) manufacturing, laser processes, electron beam processes, surface microtexturing, nanotechnology, and metal-injection molding (MIM) powder metallurgy techniques[13–16], resulting in increasing application areas for titanium materials. As for biomaterials, reflecting a

natural demand for allergy-free metallic materials composed of nontoxic elements, research and development in metallic biomaterials, dental, and healthcare materials have advanced remarkably [17,18].

Due to various characteristic properties associated with titanium and titanium-based alloys, different types of dental and medical prostheses have been developed and are currently being utilized. They include cardiac devices (especially mechanical heart valves, pacemakers, stents), operational devices and equipment, and orthopedic implants. In the dental field, the list expands to specifically orthodontic brackets and wires, dental implants, prosthetic appliances, and endodontic files.

It is well recognized that the first reaction of a vital hard/soft tissue (i.e., *host tissue*) to any type of biomaterial (ceramics, polymers, metals and alloys, composites) is a rejection; accordingly, biomaterial is normally recognized as a “*foreign material*” by the host tissue. The biological acceptance of these foreign materials by the living tissues is essentially controlled by the surface and interfacial reaction between the organic substance and the inorganic substrate. The surface is not just a free end of a substance, but it is also a contact and boundary zone with other substances (either in gaseous, liquid, or solid). A physical system composed of a homogeneous component such as solid, liquid, or gas and clearly distinguishable from each other is called a phase, and a boundary at which two or three of these individual phases are in contact is called an interface. Surface and interface reactions include reactions with organic or inorganic materials, vital or nonvital species, and hostile or friendly environments. Surface activities may vary from mechanical actions (fatigue crack initiation and propagation, stress intensification), chemical action (discoloration, tarnishing, contamination, corrosion, and oxidation), mechanochemical action (corrosion fatigue and stress-corrosion cracking), thermomechanical action (thermal fatigue), tribological and biotribological actions (wear and wear debris toxicity, and friction) to physical and biophysical actions (surface contact and adhesion, adsorption, absorption, diffusion, cellular attachment, etc.). Accordingly, the longevity, safety, reliability, and structural integrity of dental and medical materials are greatly governed by these surface phenomena, which can be detected, observed, characterized, and analyzed by virtue of various means of devices and technologies [8,19].

Interfaces are as important as surfaces. They can be found in various combinations, such as dentin/resin bonding, post/lute/tooth system, implant/hard tissue system, and metal coping/porcelain system. A common phenomenon underlying these interfacing couples includes the fact that there is always an intermediate layer between two distinct bodies. Accordingly, there are two bodies with one (intermediate) interface. For example, when porcelain is fired on a metal coping, the resultant interface between them is normally considered an interdiffusion layer in which elements from both the porcelain and the metal coping are involved. The stability, bonding or adherent strength, and the structural integrity of these systems are strongly reliant on the interfacial behaviors under various mechanical and/or chemical environments and actions.

To determine the compatibilities (biological, mechanical, and morphological) of a biomaterial to receiving human hard/soft tissue, it is also important to understand

the interfacial phenomena between the biomaterial and the biological system into which the material is to be implanted [19]. At such an interface, the molecular constituents of the biological system meet and interact with the molecular constituents of the surface of the biomaterials [20]. Since these interactions occur primarily on the molecular level and in a very narrow interface zone having a width of less than 1 nm ($1 \text{ nm} = 0.001 \text{ } \mu\text{m} = 0.1 \text{ } \text{\AA}$), surface properties are on an atomic scale, and in particular the composition and structure of surface layers of the biomaterial may play an important role in interfacial phenomena [19]. Hence, surface and interface characterizations and their biochemical and biomechanical roles in biological environments are one of the most important portions of this book. Of interest and as will be seen in later chapters (particularly in Chapters 6 and 7), scientific approaches to, characterization of, and interpretation of such interfacial layers differ between materials scientists, and bioscientists and clinicians; the former tend to investigate the interface layers from the materials perspective, whereas the latter observes them from the living tissue perspective. Unfortunately, there is no single report that compiles results obtained from both material science side and biological side.

It has been noted that hazardous substances are used with relative safety in dentistry when their identity is known, such as mercury in dental amalgam and strong acids in cements and etching agents [20]. The following species and elements can be added to this category: beryllium in cements and alloys, asbestos in periodontal packs and drug solutions, lead in impression materials, and cadmium in silver solders and temporary crowns. Alloys containing Cr, V, and Ni (which are known to exhibit heavy metal toxicity) are known to be carcinogenic in animals and humans, with local and systemic dissemination of released metallic ions in the tissues. Such examples indicate a need for full scientific consideration of the biological effects of materials at an early stage of development when the implications of use of certain ingredients or techniques may be recognized [21]. It can be clearly recognized, currently, that most of the materials or elements mentioned above are totally or partially eliminated from their original contents.

In this evidence-based overview book, accordingly, a general characterization of titanium materials as well as their various actions (mechanical, tribological, biotribological, chemical, biochemical, electrochemical, thermal, mechanochemical, biological, etc.), types of application, fabrication technologies, the surface/interface characterization of implants, and new and advanced materials and technologies for dental/medical titanium will be covered. In the second edition, macro-, micro-, and nano-texturing of titanium surfaces, tissue engineering-related materials including scaffolds, and functionally graded materials and structures are extensively included and analyzed.

References

- [1] Lautenschlager EP, Monaghan P. Titanium and titanium alloys as dental materials. *Int Dent J* 1993;43:245–53.
- [2] Narayan RJ, Roeder RK. The development of novel materials for medical devices. *J Met* 2009;61:13.

- [3] Zivić F, Babić M, Grujović N, Mitrović S. Tribometry of materials for bioengineering applications. *Tribol Indust* 2010;32:25–32.
- [4] Black J, Hastings JG, editors. *Handbook of biomaterial properties*. UK: Chapman & Hall, Thomson Science; 1998.
- [5] Nychka JA, Gentleman MM. Implications of wettability in biological materials science. *J Met* 2011;63:39–48.
- [6] Roeder RK. A paradigm for the integration of biology in materials science and engineering. *J Met* 2011;63:49–55.
- [7] Moore BK, Oshida Y. Materials science and technology in dentistry. In: Wise DL, Trantolo DJ, Altobelli DE, Yaszemski MJ, Gresser JD, Schwartz ER, editors. *Encyclopedic handbook of biomaterials and bioengineering*. New York, NY: Marcel Dekker Inc.; 1995. pp. 1325–430 [chapter 48]
- [8] Allen P. Titanium alloy development. *Adv Mater Process* 1996;154:35–7.
- [9] Tuominen S, Wojcik C. Alloys for aerospace. *Adv Mater Process* 1995;153:23–6.
- [10] Ratner BD, Johnston AB, Lenk TJ. Biomaterials surfaces. *J Biomed Mater Res* 1987;21:59–90.
- [11] Loiacono C, Shuman D, Darby M, Luton JG. Lasers in dentistry. *Gen Dent* 1993;42:378–81.
- [12] Singh J. The constitution and microstructure of laser surface-modified metals. *J Met* 1992;34:551–62.
- [13] Froes FH. Titanium—Is the time now? *J Met* 2004;56:30–1.
- [14] Faller K, Froes FH. The use of titanium in family automobiles: current trend. *J Met* 2001;53:27–8.
- [15] Kosaka Y, Fox SP, Faller K. Newly developed titanium alloy sheets for the exhaust systems of motorcycles and automobiles. *J Met* 2004;56:32–4.
- [16] Kearns M. Titanium: alive, well and booming!. *Adv Mater Process* 2005;163:63–4.
- [17] Roncone K. A conversation with titanium suppliers and end users. *J Met* 2005;57:11–3.
- [18] Niionomi M, Hanawa T, Narushima T. Japanese research and development on metallic biomedical, dental, and healthcare materials. *J Met* 2005;57:18–24.
- [19] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones—Toward a morphological compatibility of implants. *J Bio-Med Mater Eng* 1994;4:397–407.
- [20] Kasemo B, Lausmaa J. Surface science aspects on inorganic biomaterials. *CRC Crit Rev Biocompatib* 1986;2:335–80.
- [21] Smith DC. The biocompatibility of dental materials. In: Smith DC, Williams DF, editors. *Biocompatibility of dental materials, volume 1: characteristics of dental tissues and their response to dental materials*. Boca Raton, FL: CRC Press Inc.; 1982. pp. 1–37.

This page intentionally left blank

2 Materials Classification

2.1 Introduction

Materials research, development, and application should include needs- and seeds-oriented approaches. A good example of *needs-oriented materials* R&D is the search for a lightweight structural material (particularly demanded by aerospace industries). This has accelerated the development of titanium alloys. Increased use of titanium alloys as biomaterials is occurring due to their lower modulus, superior biocompatibility, and enhanced corrosion resistance when compared to more conventional stainless steels and cobalt-based alloys. These attractive properties were a driving force for the early introduction of a CpTi (commercially pure titanium) and $\alpha + \beta$ alloy such as Ti–6Al–4V, as well as for the more recent development of new Ti-based alloy compositions and orthopedic metastable β -titanium alloys. The latter possess enhanced biocompatibility, reduced elastic modulus, and superior strain-controlled and notch fatigue resistance. However, the poor shear strength and wear resistance of titanium alloys have nevertheless limited their biomedical use. Although the wear resistance of β -Ti alloys has shown some improvements when compared to $\alpha + \beta$ alloys, the ultimate utility of orthopedic titanium alloys as wear components will require a more complete fundamental understanding of the wear mechanisms involved [1]. On the other hand, NiTi provides a typical example of *seeds-oriented material*. Opposing its initial specific aim for development (which was a strategic search for submarine structural materials with a relatively low-damping capacity), its unique shape-memory effect (SME), as well as superelasticity (SE) properties, needed a successful application. This was realized when it was used for medical applications (orthopedic implants, stents, Harrington bars, ENT [ear, nose and throat] applications such as otorhinolaryngology implants, maxillofacial prostheses, and dental applications such as blade-type implants, orthodontic wires, splints, and endodontic files).

Owing to recent advances in quantitative metallography, as well as molecular/atomic dynamics and designing concepts, these two needs- and seeds-oriented concepts have been integrated systematically to develop nanoscale materials designs and manufacturing technologies. In addition, owing to advanced powder metallurgy (such as MIM: Metal Injection Molding), a unique material design can be achieved, sometimes without the difficulties of melting procedures.

2.2 General Classification

Basically, titanium and titanium-based alloys can be classified into α type (HCP: hexagonal-closed packed crystalline structure), near α type, ($\alpha + \beta$) type, and β type (BCC: body-centered cubic crystalline structure) alloy groups. Alloying elements added to titanium are divided into two groups: alpha (α) stabilizers and beta (β) stabilizers. Elements, such as Al, Sn, Ga, Zr, and interstitial elements (either singly of C, O, and N or in combination), dissolve into the titanium matrix and are strong solid solution strengtheners which produce little change at the transformation temperature (β -transus: 885°C for pure Ti) from the HCP (α) to the BCC (β) structure of pure titanium when heating and from BCC to HCP when cooling. Hence, they are known as α -stabilizers and exhibit good high-temperature performance. Alloying elements that decrease this phase transformation temperature are referred to as β -stabilizers. Generally, β -stabilizing elements are the transition metals, such as V, Mo, Nb, Ta, and Cr, providing much friability [2]. Besides these alloying elements, Fe, Cu, Ni, Si, and B are frequently added to Ti-based alloys for improving mechanical strength, chemical stability, castability, and/or grain refining. By increasing the α -phase portion, it is generally recognized that (1) β -transus temperature increases, (2) creep strength as well as high-temperature strengths enhance, (3) flow stress increases, and (4) weldability improves. By increasing the β -phase portion, it is known that (1) room temperature strength increases, (2) heat-treatment and forming capabilities enhance, and (3) strain-rate sensitivity increases so that superplastic forming (SPF) is more favorably applicable. Table 2.1 summarizes the above discussion.

The titanium industry is rebounding with projections that the worldwide mill product shipments by 2008 was about 56,000 tons per year (up from the 43,000 tons per year of 2002/2003), due to the increase in commercial airplane production along with increased sales to the military, industrial, and consumer markets. As always, cost remains the major barrier to ore titanium use, especially in the industrial and consumer markets. However, there are new reduction processes being developed and lower cost fabrication processes ready for implementation such as the powder-metallurgy approaches [3]. Numerous attempts have been undertaken in the last 60 years to reduce the cost of producing titanium [4]. Primary titanium can be produced from a number of feed materials using different reduction reactions. Depending on the process, many physical forms of titanium can be produced. The different feed materials that can be used include slag or rutile (TiO_2); potentially acceptable for producing ferro-titanium alloys are high-purity TiCl_4 , TiI_4 , and Na_2TiF_6 . Depending on the process used, the following forms of titanium are produced: titanium sponge, sintered electrode sponge, powder, molten titanium, electroplated titanium, hydride powder, and vapor-phase deposited titanium. The process of electrowinning molten titanium dioxide is conceptually the same as the Hall–Héroult process to produce aluminum from alumina. The oxide is dissolved in a molten salt electrolyte at a sufficiently high temperature so that when it is reduced, molten metal settles out of the electrolyte. The feed is introduced

Table 2.1 Three Major Types of Titanium Materials and Influencing Effects of Major Alloying Elements

Type/Material Property	α and near α	$\alpha + \beta$	Near β and β
α stabilizing elements	Al, Sn, Ga, Zr, C, O, N		V, Mo, Nb, Ta, Cr
β stabilizing elements			
Typical materials	Commercially pure Ti	Ti—5Al—2.5Fe	Ti—3Al—8V—6Cr—4Mo—4Zr
	Ti—5Al—2.5Sn	Ti—5Al—2Mo—2Fe	Ti—4.5Al—3V—2Mo—2Fe
	Ti—5Al—6Sn—2Zr—1Mo	Ti—5Al—3Mo—4Zr	Ti—5Al—2Sn—2Zr—4Mo—4Cr
	Ti—6Al—2Sn—4Zr—2Mo	Ti—5Al—2.5Fe	Ti—6Al—6Fe—3Al
	Ti—8Al—1Mo—1V	Ti—6Al—7Nb	Ti—10V—2Fe—3Al
		Ti—6Al—4V	Ti—13V—11Cr—3Al
		Ti—6Al—6V—2Sn	Ti—15V—3Cr—3Al—3Sn
		Ti—6Al—2Sn—4Zr—6Mo	Ti—35V—15Cr
			Ti—8Mo—8V—2Fe—3Sn
			Ti—11.5Mo—6Zr—4.5Sn
			Ti—30Mo, Ti—40Mo
			Ti—13Nb—13Zr
			Ti—25Pd—5Cr
			Ti—20Cr—0.2Sn
			Ti—30Ta

(Continued)

Table 2.1 (Continued)

Type/Material Property	α and near α	$\alpha + \beta$	Near β and β
β -transus temperature	Higher $\leftarrow$ lower		
Specific density	Lower $\rightarrow$ higher		
Room temperature strength	$\rightarrow$		
Room temperature toughness	$\rightarrow$		
MOE	$\leftarrow$		
Machinability	$\leftarrow$		
Age hardenability	$\rightarrow$		
Heat resistance	$\leftarrow$		
Weldability	$\leftarrow$		
High temperature strength	$\leftarrow$		
Heat treatability	$\rightarrow$		
Plastic formability	$\rightarrow$		
Strain-rate sensitivity	$\rightarrow$		
Superplastic formability	$\rightarrow$		
Creep resistance	$\leftarrow$		

Note: this chart does not include TiNi, Ti₃Al (α_2) and TiAl (γ) intermetallic type alloys.

continuously, and the product is recovered periodically from the cell or pot [5]. The magnesium reduction reaction of $\text{TiCl}_4\text{--MgCl}_2$ has been shown to produce titanium metal where the $\text{TiCl}_4\text{--MgCl}_2$ was synthesized through the reaction of seed titanium in molten MgCl_2 and TiCl_4 gas. The macroscopic shape of the titanium product and its microscopic morphology depend on reduction temperature. Titanium metal thus obtained was then button melted in an arc furnace. It appears that the titanium metal product obtained is suitable for its powder as well as melted product applications [6].

When any titanium material possesses either one of the aforementioned types as a major constitutional phase, it is named after the type of phase.

Alpha alloys: Alpha alloys generally have creep resistance superior to that of beta alloys and are preferred for high-temperature applications. The absence of a ductile–brittle transition (a feature of beta alloys) makes alpha alloys suitable for cryogenic applications, too. Unlike beta alloys, alpha alloys cannot be strengthened by heat treatment because the alpha structure is a stable phase.

Alpha + beta alloys: Alpha + beta alloys have compositions of a mixture of α and β phases and may contain between 10% and 50% beta phase at room temperature. The most common type within this group alloy is Ti–6Al–4V*. Within the alpha + beta type class, an alloy containing much more alpha than beta is often called a near-alpha alloy. Generally, when strengthening is needed, the alloys are rapidly cooled (i.e., quenched) from a temperature high in the alpha–beta range above the β -transus. This solution treatment is followed by an intermediate-temperature treatment (aging) to produce an appropriate mixture of alpha and transformed beta products.¹

Beta alloys: Beta titanium has a wider solubility for alloying elements without precipitating any intermetallic compounds. Beta alloys contain transition elements such as V, Mo, Nb, Ta, and Cr, which tend to reduce the temperature of the $\alpha \leftrightarrow \beta$ phase transformation (or simply β -transus). They have excellent forgeability over a wider range of forging temperature than α alloys, and β -alloy sheet is cold formable in the solution-treated condition. Beta alloys have excellent work-hardening and heat-treatment capabilities. A common thermal treatment involves solution treatment followed by aging at temperatures ranging from 450°C to 650°C [7]. Beta alloys are one of the most promising groups of titanium alloys in terms of processing, properties, and potential applications. This group of alloys (including beta,

¹ Note: Ti–6Al–4V indicates the Ti-based alloy added with 6 wt% (or w/o) of Al and 4 wt% of V. The text uses this alloy description; otherwise if at.% (a/o) is used, both a/o and w/o will be indicated. For conversion between w/o and a/o, let W_X and A_X be weight % and atomic % of element X in the X–Y binary alloy, where X and Y are atomic weights of the respective elements. For each of the respective elements, conversion from w/o to a/o and from a/o to w/o is calculated as follows:

$$A_X = 100/[1 + (X/Y)\{(100/W_X) - 1\}] \text{ and } A_Y = 100 - A_X$$

$$W_X = 100/[1 + (Y/X)\{(100/A_X) - 1\}] \text{ and } W_Y = 100 - W_X$$

metastable beta, and beta-rich alpha/beta compositions) represents the highest range of strength, fatigue resistance, and environmental resistance among all titanium materials.

Advantages and disadvantages of beta Ti alloys are listed as follows. (1) While beta alloys offer the highest strength-to-weight ratios of any Ti alloys, they are nonetheless higher in density compared to other alloys. Densities on the order of 4.70–4.98 are typical, with ultimate strength levels in the 1517–1586 MPa (or 1.52–1.59 GPa) range. (2) In the solution-treated condition, values of modulus of elasticity (MOE) from 69 to 76 GPa are typical, and in the aged condition, MOE values of 103–110 GPa are common. In some cases, such as medical implants, matching the low modulus of bone is important (to achieve the mechanical compatibility). (3) Although beta alloys are expensive to formulate, the strip-rollable alloys can take advantage of low-cost/high-yield cold strip processing versus hot band mill operation. (4) Although segregation can be a problem during melting (solidification), the rapid cooling rate obtained in most weldments often prevents transformation and improves weldability. (5) Beta-phase alloys typically exhibit outstanding cold formability. However, their low-elastic modulus and high strength can often result in a high springback, which must be accounted for in orthodontic archwires. Because of the high degree of stability of the beta phase, a water quench is often not required for solution treating; air cooling greatly reduces distortion, as does low temperature for solution treatment. However, beta alloys are notorious for surface oxygen contamination even in supposed vacuum heat treatments, so care is needed to remove such contamination; usually the contamination is removed by pickling. (6) While beta alloys usually exhibit excellent fill characteristics during casting, segregation may limit the utility of some alloys. (7) Beta-phase alloys are generally not considered for elevated or cryogenic temperature service. Also, many beta alloys have outstanding corrosion resistance. Generally, corrosion resistance increases with molybdenum content, as the 316 (18Cr–8Ni–2Mo) stainless steel exhibits better resistance against the pitting corrosion than the 304 (18Cr–8Ni) stainless steel. Accordingly, new types of titanium, such as gamma alloys (e.g., 46Ti–48Al alloy with Ti₃Al and TiAl phases), were developed [8–11]. There are still strong areas in developing V-free Ti materials [12–14].

In these alloys, the single α -phase and single β -phase regions are separated by a two-phase ($\alpha + \beta$) region. As a result, the alloys utilize multicomponent elements and are composed of mixtures of α and β stabilizers. Depending on the ratio of α and β phases, they can be furthermore subgrouped into near (α) and near (β) alloys. Typical beta group Ti alloys include (1) beta type (Ti–35V–15Cr, Ti–40Mo, Ti–13V–11Cr–3Al, Ti–3Al–8V–6Cr–4Mo–4Zr, Ti–30Mo), metastable beta type (Ti–6V–5.7Fe–2.7Al, Ti–12V–11Cr–3Al, Ti–1Al–8V–5Fe, Ti–12Mo–6Zr–2Fe, Ti–4.5Fe–6.8Mo–1.5Al, Ti–15V–1Mo–0.5Nb–3Al–3Sn–0.5Zr, Ti–3Al–8V–4Mo–4Zr, Ti–15Mo, Ti–8V–8Mo–2Fe–3Al, Ti–15Mo–2.6Nb–3Al–0.2Si, Ti–15V–3Cr–3Sn–3Al, Ti–11.5Mo–6Zr–4.5Sn, Ti–10V–2Fe–3Al, Ti–5V–5Mo–1Cr–1Fe–5Al, Ti–5Al–2Sn–4Mo–4Cr, Ti–4.5Al–3V–2Mo–2Fe), and beta-rich group (Ti–5Al–2Sn–2Cr–4Mo–4Zr–1Fe, Ti–13Nb–13Zr, Ti–4.5Al–3V–2Mo–2Fe) [15–18].

2.3 Medical/Dental Titanium Materials

Currently, pure titanium and $\alpha + \beta$ type Ti–6Al–4V ELI (extra low level of interstitial content) alloys are widely used as structural and/or functional biomaterials for the replacement of hard tissues in devices such as artificial total hip or knee replacements and dental implants, since they exhibit excellent specific strengths and corrosion resistance, and the best biocompatibility characteristics among metallic biomaterials. They are used more than any other titanium biomaterials; however, other new titanium alloys for biomedical applications have now been included in ASTM standardizations [19,20]. For example, β -type Ti–15Mo [21] has been registered in ASTM standardizations, and β -type Ti–35Nb–7Zr–5Ta [22] and $\alpha + \beta$ type Ti–3Al–2.5V [23] are in the process of being registered.

Among several dozen commercially available alloys, the following are typical titanium materials which are utilized or have been experimentally and clinically tried in both the medical and dental fields.

2.3.1 Commercially Pure Titanium

Under the category of “unalloyed grades” of ASTM specification, there are five materials classified in this group; they include ASTM grade 1 (99.5% Ti), grade 2 (99.3% Ti), grade 3 (99.2% Ti), grade 4 (99.0% Ti), and grade 7 (99.4% Ti). Although each material contains slightly different levels of N, Fe, and O, C is specified <0.10 wt% (wt% or w/o) and H is also specified <0.015 wt%. ASTM CpTi grades 1–4 (unalloyed titanium) allow a hydrogen content up to 0.015 wt% (i.e., 15 ppm). It was reported that if CpTi contains more than 250 ppm of hydrogen, the material would be susceptible to stress corrosion cracking (SCC) and hydrogen embrittlement [24].

Grade 1: Grade 1 CpTi is the lowest strength unalloyed titanium with a slightly lower residual content. Both oxygen and iron residuals improve the impact strength. Oxygen acts as an interstitial strengthener, maintaining a single α -phase HCP microstructure. Iron acts as a second β phase BCC grain refiner, offering moderate strengthening capabilities. The lower residual content makes grade 1 the lowest strength CpTi grade, but it has the highest ductility with an excellent cold formability.

Grade 2: The grade 2 is the most frequently selected titanium grade in industrial service having well-balanced properties of both strength and ductility. The strength levels are very similar to those of common stainless steel and its ductility allows for good cold formability.

Grade 3: CpTi grade 3 possesses a slightly higher strength due to its slightly higher residual content (primarily oxygen and also nitrogen) with slightly lower ductility.

Grade 4: The grade 4 is the highest strength grade of the CpTi series; it serves mainly in the aerospace/aircraft industry.

For all CpTi grades 1–4, the 0.2% off-set equivalent-yield strength ($\sigma_{0.2YS}$) and the ultimate tensile strength (σ_{UTS}) appear well correlated to oxygen contents [25].

Through linear regression analysis, with the oxygen content expressed by [O], it was found that $\sigma_{0.2YS} = 1336.2 \times [\text{O}] - 66.7$ in MPa with r (correlation coefficient) of 0.9865, and $\sigma_{UTS} = 1351.5 \times [\text{O}] - 3.7$ in MPa with r of 0.9946.

By far the most widely used of the CpTi grades is grade 2 [25]. From this base, the other grades have been developed for better formability or higher strength levels, significantly increasing corrosion resistance at higher temperatures, and/or improving corrosion resistance at lower pH (or higher acidity) levels [26]. There is a distinct difference in using CpTi between industry and medicine. Among various applications of CpTi materials in dental and medical fields, the dental CpTi implant is the most frequently and widely employed. Information on CpTi grade selection for dental application indicates that, despite the popularity of grade 2 in industry [23], grades 3 and 4 are equally selected in most of the 20 major dental implant systems. Only two companies use grades 1 and 2 [27–30]. More interesting, however, are their availabilities. In preparing CpTi grades 1–4 for corrosion resistance comparisons, Hernandez [27] searched 14 material suppliers but found that only 2 out of the 14 suppliers were able to provide all four grades. Grades 2 and 4 were available without any problems, whereas CpTi grade 3 is the least popular and is difficult to obtain; 2 out of the 14 suppliers were able to provide CpTi grade 3. After conducting electrochemical corrosion testing, using 37°C Ringer’s solution as an electrolyte, it was found that CpTi grade 3 exhibited the least corrosion resistance. Regardless of material availability [27,28], this supported the unpopularity of CpTi grade 3. Hence, despite the popularity and availability of grade 2 in industries, CpTi grade 2 is the least popular, although its corrosion resistance is somewhat superior to grade 3, which is the worst grade in terms of corrosion resistance among the four grades.

2.3.2 Ti–6Al–4V

This alloy belongs to the $\alpha + \beta$ phase alloy group and is particularly popular because of its high-corrosion resistance and the reputed low toxicity of ions released from the surface due to dense and protective passive oxide (which is mainly TiO_2) film formation. Ti–6Al–4V (which is, in some articles, marked as Ti-6/4) exhibits good mechanical and excellent tissue compatibility properties that make it well suited for biomedical applications where a bone anchorage is required, particularly for implant applications [30]. Ti–6Al–4V ELI is also available and employed in the medical area [31].

SPF of Ti–6Al–4V, with a standard grain size of about $8\text{ }\mu\text{m}$, is typically performed between 900°C and 920°C . But if the grain size is reduced to $1\text{ }\mu\text{m}$, Ti–6Al–4V can exhibit excellent SPF performance at around 775°C . Since this material shows excellent self-diffusion bonds at solid state, as do other standard grain size titanium alloys at this temperature, SPF and SPF/DB (diffusion bonding) hardware can be produced. There are several advantages to using this lower temperature, including a smaller amount of alpha case developed on parts, longer press platen and heater life, and less oxidation of the tool surface [32].

2.3.3 *Ti–6Al–7Nb*

As a result of searches for vanadium-free Ti–6Al–4V equivalent alloys, this alloy was developed to enhance the wear resistance [33] and castability [34]. The optimal composition was found to be Ti–6Al–7Nb (or simply Ti-6/7). This custom-made alloy designed for implants shows the same alpha/beta structures as Ti–6Al–4V and exhibits equally good mechanical properties. The corrosion resistance of Ti–6Al–7Nb in sodium chloride solution was evaluated to be equivalent to that of pure titanium and Ti–6Al–4V, due to formation of a very dense and stable passive layer. Highly stressed anchorage stems of different medical prostheses (including hip, knee, and wrist joints) have been made from hot-forged Ti–6Al–7Nb. The surfaces of these Ti–6Al–7Nb prostheses were further hardened by means of a very hard 3–5 μm thick titanium nitride coating or by oxygen diffusion hardening to a depth of 30 μm , in order to enhance the biotribological properties [35].

The shear bonding strength and leakage of heat-polymerized denture base resin to Ti–6Al–7Nb and Co–Cr castings were evaluated using four adhesive systems. It was reported that (i) thermocycling significantly decreased bonding strength and promoted dye penetration, (ii) with the application of adhesive systems, postthermocycling bond strength was significantly improved and dye penetration was inhibited, and (iii) the bonding strength of Ti–6Al–7Nb was significantly smaller than that of Co–Cr alloy with marginal differences [36].

2.3.4 *Ti–3Al–2.5V*

Ti–3Al–2.5V alloy possesses an excellent ductility and cold formability, allowing it to be cold worked by standard tube-making processes and bent for installation. It is easily welded and may be heat treatable to a wide range of strengths and ductility [37].

2.3.5 *Ti–5Al–3Mo–4Zr*

A newly developed titanium for surgical implant application, Ti–5Al–3Mo–4Zr (or simply referred to Ti-5/3/4), was evaluated, and its properties were compared with conventional biomaterials. Mechanical properties and metallic ion elution were also examined. It was reported that the new alloy is advantageous over Ti–6Al–4V ELI because it does not contain biohazardous alloying elements (e.g., vanadium) and has superior mechanical properties to stainless steel. Corrosion abrasive wear resistance is also improved in Ti–5Al–3Mo–4Zr. As a result, newly designed artificial hip joints were fabricated with this alloy [37,38].

2.3.6 *Ti–5Al–2.5Fe*

In the course of developing a vanadium-free titanium-based alloy, the another new alloy Ti–5Al–2.5Fe (which is $\alpha + \beta$ phase alloy) has been developed to avoid the

presence of toxic vanadium, which is an alloying element in the Ti–6Al–4V alloy and may increase to more than 15% in the β phase. Hip prostheses and hip prosthesis heads were fabricated from the Ti–5Al–2.5Fe alloy with a grain size of 20 μm or less. The frictional biotribological behavior of a hip prosthesis head in contact with an ultrahigh molecular weight polyethylene (UHMWPE) cup was investigated. It was shown that (i) the frictional behavior of a head coated with an oxide layer about 1–3 μm thick produced by induction heating of the surface was equal to that of a head fabricated from alumina ceramics and (ii) the oxide layer was still present after 10^7 cycles in 0.9% NaCl solution, indicating excellent corrosion resistance of this alloy [39].

2.3.7 Ti–5Al–2Mo–2Fe (SP700)

Ti–6Al–4V is the most widely used titanium alloy. However, Ti–6Al–4V still suffers from limited applications in nonaerospace fields compared to CpTi, aluminum alloys, and steels. The reasons for this include (1) poor hot-workability, with a normal hot-working temperature range that is too high and too narrow, (2) poor cold-workability that virtually prohibits cold-working, (3) poor hardenability that is frequently inconsistent, and (4) a high superplastic forming temperature of around 900°C that results in rapid die wear. To overcome these disadvantages associated with Ti–6Al–4V, a new beta-rich alpha-beta duplex phase titanium alloy has been developed, called SP700, since the newly developed Ti alloy remarkably exhibits high-superplastic capability at operating temperatures around 700°C. It was reported that SP700 provides excellent hot- and cold-workability, as well as greatly improved superplastic forming characteristics (i.e., the strain rate sensitivity exponent, m -value, is about 1.0, indicating that flow is close to that of a Newtonian viscous flow), high strength, and high toughness. Dental denture bases have been fabricated using this SP700 alloy by using a superplastic forming technique [40].

2.3.8 Ti–Ni

Historically, the NiTi alloy was developed when the US Navy was searching for a new submarine material exhibiting good damping capacity. Buehler, who conducted the bending tests on NiTi alloys, discovered that a large deformation was completely recovered by a slight heating to return to its original shape. This phenomenon is later referred to as a SME. Since the test was performed and the material was developed at the US Naval Ordnance Laboratory, this unique material is called as NITINOL (Nickel–Titanium Naval Ordnance Laboratory) [41]. This material is also often called and marked as NiTi, TiNi, or Nitinol. In this book, since the Ni element contains more than 50 w/o (weight percentage), the term “NiTi” is used according to the ordinal way of describing alloy systems in the conventional metallurgy.

It is well known that this alloy exhibits unique phenomena such as SME as well as SE. By SME, a material first undergoes a martensitic transformation. After deformation in the martensitic condition, the apparently permanent strain is

recovered when the specimen is heated to cause the reverse martensitic transformation. Upon cooling, it does not return to its deformed shape. When SME alloys are deformed in the temperature regime a little above the temperature at which martensite normally forms during cooling, a stress-induced martensite is formed. This martensite disappears when the stress is released, giving rise to a superelastic stress–strain loop with some stress hysteresis. This property applies to the parent phase undergoing a stress-induced martensitic transformation. The other unique property associated with NiTi is SE. When SME alloys are deformed, a superelastic alloy deforms reversibly to very high strains up to 10% by the creation of a stress-induced phase. When the load is removed, the new phase becomes unstable and the material regains its original shape. Unlike SME alloy, no change in temperature is needed for the alloy to recover its initial shape. The term *pseudoelasticity* is a more generic term that encompasses both superelastic and rubberlike behavior [42].

Because of the uniqueness of SME and the SE associated with NiTi, there have been many applications in both the industrial and dental/medical fields, including dental and orthopedic implants, artificial heart valves, stents, endodontic files, orthodontic archwires, etc. [43–48]. Superelastic devices take advantage of their large, reversible deformation; their applications are not limited to medical/dental fields but can also be found in parabola antenna used on space shuttles, frames for eyeglasses, and sporting goods such as fishing line.

Major applications of SE TiNi alloy can be found in orthodontics—particularly archwires. Bourauli et al. [49] studied fatigue failure of as-received and retrieved TiNi archwires. It was found that (i) retrieved wires fractured at a significantly lower number of fatigue cycles compared to their as-received wires and (ii) the size of wires played a role in determining fracture with larger cross-sections showing reduced fatigue failure properties and 0.30 and 0.035 mm specimens showing no fracture at the selected strain and number of cycles.

Surface topology and corrosion behaviors of TiNi were investigated in (1) fluoride mouthwashes and in artificial saliva with addition of commercially fluoride tooth paste or prophylactic gels [50], (2) artificial saliva at 5°C, 24°C, 37°C, and 45°C [51], and (3) artificial saliva for SCC study [52]. It was reported that (i) in artificial saliva added with high-fluoride prophylactic gel (about 17,000 ppm), a significant increase in surface roughness was found [50], (ii) corrosion current density increased with temperature and showed an incidence of pitting [51], and (iii) the SCC process under the constant loading tests depended on the pH value of saliva and applied stress [52].

Phase transformation was investigated statically [53] and under an influence of thermocycling [54] and applied load [55]. It was reported that (i) with increased thermocycling the extent of R-phase in the heating peaks decreased in 35°C NiTi and an austenite to martensite peak shoulder developed during cooling in 27°C NiTi [54] and (ii) the transformation behavior of TiNi wires with change in temperature was affected by application of tensile load [55].

Another typical application of SE TiNi alloys is endodontic rotary instruments (including files and reamers). In case of the need for autoclave sterilization or other processes, the effects of additional heat treatment should be important in order to

determine any possible changes in SE characteristics [56]. It was found that heat treatments at 400°C, 500°C, and 600°C raised the A_f (austenite transformation finish) temperature in a range from 45° to 50°C, and heat treatment at 850°C caused drastic changes in transformation behavior [56]. Simulating the actual mechanical movement, low cycle fatigue of NiTi rotary instruments was investigated [57–59]. It was reported that (i) the low-cycle fatigue behavior is not affected by the cross-sectional shape of the instrument and there appears to be a critical extent of crack propagation for various surface strain amplitudes leading to final catastrophic fracture of the instrument [58] and (ii) there was a sequential decrease in deflection load during the rotation [59].

The development of gap-free abutments is a challenging problem, because a gap between the implant and the abutment, which is a consequence of current manufacturing limitations, can serve as a reservoir for pathogens, leading to peri-implantitis [60]. The abutment prototypes were tested for their susceptibility to microbes *in vitro* by contaminating the abutments before assembly using a bacterial solution. It was demonstrated that dental implants fabricated with gap-free abutments using SME alloy showed significantly reduced bacterial leakage versus conventional implants, and this improvement could minimize clinical problems such as peri-implantitis and consequently enhance the long-term success of dental implants [60].

In the medical area, research works can be found for articular prostheses [61] and stents for colon construction [62]. Bearing in mind potential applications of NiTi alloy as stent or defect closures, Shabalovskaya et al. [63] evaluated the comparative fibrinogen adsorption and platelet morphology on a wide array of NiTi surfaces (polished, chemically etched, boiled in water, electropolished in different electrolytes, and heat treatments). It was observed that treated surfaces (with natures of various topographies and crystallinity from mostly amorphous to nanocrystalline with Ni concentration from 1% to 8%) induced Ni release into a biological medium in a subtoxic range (0–11 ng/ml/cm²), and fibrinogen adsorption to NiTi surfaces ranged from that characteristic to pure Ni (130 ng/ml/cm²) to pure Ti (300 ng/ml/cm²). It was concluded that by using appropriate surface treatments, the thrombogenicity of NiTi can be manipulated to satisfy both the requirements for stents and defect closures [63].

The superelastic nature of bones requires matching biomechanical properties from the ideal artificial biomedical implants in order to provide smooth load transfer and foster the growth of new bone tissues. This is called mechanical compatibility and is one of the three major compatibilities (biological and morphological are other two) requirements for successful implant practice, as the present author has proposed and described in Chapter 6 of this book. Liu et al. [64] determined the biomechanical characteristics of porous NiTi implants and investigated bone ingrowth under the actual load-bearing conditions *in vivo*. Porous NiTi, porous Ti, dense NiTi, and dense Ti were implanted in the distal part of the femur/tibia of rabbits for 15 weeks. The bone ingrowth and interfacial bonding strength are evaluated by histological analysis and a push-out test. It was observed that the porous NiTi materials bond very well to newly formed bone tissues, and that the highest average

strength of 357 N and best ductility are achieved from the porous NiTi materials. The bonding curve obtained from the NiTi scaffolds shows similar SE to that of natural bones with a deflection of 0.30–0.85 mm thus shielding new bone tissues from large load stress. It was concluded that (i) osteoblasts proliferate smoothly on the entire implant including the flat surface, embossed region, exposed area of the pores, and interconnected channels and (ii) the superelastic biomechanical properties of the porous NiTi scaffold promotes fast formation and ingrowth of new bones. Porous NiTi scaffolds are thus suitable for clinical applications under load-bearing conditions [64].

Although most dental/medical devices are made of SME alloys in the polycrystalline form, Yahia et al. [65] pointed out that the single crystal form shows several promising advantages especially concerning its mechanical performances.

TiNi is not the only Ti-based alloy exhibiting the SME. TiPd–Co alloys [66] and Ti–V–Fe–Al alloys [67] are other examples showing the shape recovery capability. The electrochemical behavior of Ti, Pd, Co, and TiPd alloys was investigated to obtain the fundamental data for evaluating the corrosion resistance of TiPd–Co alloys. The potential–time curve and anodic polarization of the casting specimen were measured in 0.9% NaCl solution at 37°C. Pd showed the highest positive value of the rest potential and Co showed the lowest negative value. The potential of Ti increased with time, and reached a fairly high value of -0.03 V after 5 h. TiPd alloys exhibited a potential between the values of Ti and Pd. In anodic polarization, an abrupt increase in current density at 1.0 V was observed for Pd. From 0.0 to 1.2 V, Ti showed a constant, small amount of current density attributed to passivity. The transpassivity (passivation breakdown) potential of the TiPd alloys was 0.55 V. Based on these findings, it was reported that TiPd–Co new shape memory alloys exhibited good corrosion resistance [12–15]. The application of TiNi for medical and dental implants has been attempted, but the toxicity of Ni is still doubtful. Shape recovery in the Ti–V–Fe–Al alloy was studied. Since this alloy contains more than 80% Ti without Ni, it seems to be biocompatible. Shape recovery in this alloy system occurred in Ti–(10.0–12.0)V–(1.5–3.0)Fe–(2.0–4.5)Al. By controlling the content ratio, shape recovery obtained in Ti–11.5V–1.7Fe–4.0Al was 92% at 60°C. A model implant with this alloy was prepared, and it was reported that an opening angle of 60° in the edge part was memorized. After treatment, an opening angle of 50° was recovered at 60°C. The corrosion resistance of Ti–11V–2Fe–3Al was evaluated by anodic polarization measurement in 1% NaCl solution at 37°C. It was found that stable passivation was maintained up to 2000 mV, while NiTi showed a transpassivity at about 1200 mV. These results suggest that this Ti–V–Fe–Al alloy system has applicability for dental implants [67]. There are several works on Ti–Ni–Cu alloy which is in β -phase titanium and normally used for fabricating orthodontic archwires [68,69].

2.3.9 Ni-Free Ti-Based Alloys, and Ti–Nb Alloys

Nickel is constituent of many dental alloys. Nickel is an allergen, but there is no evidence that individual patients are at a significant risk of developing sensitivity

due to contact with nickel-containing dental appliances and restorations. Hypersensitive reactions to nickel are only likely to occur with prior sensitization from nondental contacts and even these are rare [70]. Clinical evidence has been presented to show that small doses of nickel, for example, from dental appliances, may induce tolerance to this allergen. Hosoki et al. [71] assessed the hypersensitivity to dental materials. From July 2000 to June 2005, 212 patients suspected with dental metal allergy were patch tested with 226 reagents, including 19 ready-made patch test reagents and 9 custom-made reagents. Of these, 167 patients were female (78.8%) and 45 patients were males (21.2%). A total 148 patients (69.8%) had one or more positive patch test reactions. The most common allergens were Ni (25.0%), Pd (24.2%), Cr (16.7%), Co (15.9%), and Sn (12.5%). It was concluded that dentists and dental researchers should be concerned about the allergic potential of dental meal materials [71]. Reflecting on the aforementioned evidences of potential toxicity and allergic reaction of Ni-containing dental materials, Ni-free Ti-based SM and SME alloys have been recently developed, for example, Ti–Nb–Sn, Ti–Nb–Al, Ti–Nb–Ta, Ti–Nb–Zr, Ti–Nb–O, Ti–Nb–Pt, Ti–Mo–Ga, and Ti–Mo–Nb–V–Al alloys. As described in the following sections, it has been found that Ti–Nb binary alloys exhibit SME and SE at room temperature, and their SE properties can be considerably improved by thermomechanical treatment. It has also been found that SE properties of Ti–Nb alloys can be improved by the addition of alloying elements such as Zr, Ta, Pt, and O [72]. Newly developed and investigated Ti–Nb alloy systems are Ti–13Nb–13Zr [73], Ti–18Nb–5Mo–5Sn [74], Ti–29Nb–13Ta–3.6Zr [75], Ti–(23, 27, 31, 35)Nb–3Zr–2Ta [76], and Ti–45Nb [77,78]. Qazi et al. [18] developed a metastable β -Ti alloy (mainly Ti–35Nb–7Zr–5Ta) and solution treated it, followed by aging at 482°C. It was reported that (i) the heat-treated Ti–35Nb–7Zr–5Ta alloys exhibited 0.2% off-set yield strength of 1300 MPa with 8% elongation, due to $\omega + \beta$ and $\omega + \alpha + \beta$ phase precipitations and (ii) this enhanced strength makes the alloy a candidate for bone plates and screws.

2.3.10 Ti–Cu

Kikuchi et al. [79] found that (i) adding Cu to Ti base makes Ti–Cu alloy's elastic modulus increase due to a precipitation of intermetallic compound Ti_2Cu and (ii) copper turned out to be a moderate stiffener that gains an elastic modulus of titanium up to 20% at the copper concentration of 30 mass %. Aiming for developing an alloy for dental casting with better mechanical properties than unalloyed CpTi, Ti–Cu (Cu: 0.5–10 wt%) was cast in an argon-arc melting furnace. It was found that (i) the mean tensile strength was significantly higher than for cast CpTi and (ii) increases of 30% in the tensile strength and yield strengths of over 40% CpTi were obtained for the Ti–5Cu alloy [80].

Takada et al. [81] prepared binary Ti–Cu alloys containing 5–20 mass % Cu and evaluated the corrosion behavior of α -Ti and Ti_2Cu composing Ti–Cu alloys in 0.9% NaCl and 1% lactic acid solutions. It was reported that in both electrolytes, (i) Ti–Cu alloys showed the same anodic polarization curves as α -Ti up to 1.4 V,

(ii) precipitation of Ti_2Cu contributed to a small increase in current density in the transpassivation region, and (iii) the amount of Cu ions released from Ti_2Cu was 0.260 and 1.003 (in $\mu\text{g}/\text{cm}^2/7$ days) in 0.9% NaCl and 1% lactic acid solutions, respectively. Although these values are larger than those from α -Ti (0.038 and 0.096, respectively), they were not greater than those from type 4 gold alloy under the same conditions [81].

He et al. [82] prepared a group of Ti–60Cu–14Ni–12Sn–4M (M: Nb, Ta, Mo) alloys using arc melting and copper mold casting. The as-prepared alloys have a composite microstructure containing a micrometer-sized dendrite β -Ti(M) phase dispersed in a nanocrystalline matrix. It was reported that (i) alloys exhibit a low MOE in the range of 50–103 GPa and a high-yield strength of 1037–1755 MPa, together with large plastic strains, (ii) with addition of refractory elements, Nb, Ta, and Mo, a micrometer-sized dendritic β -phase-nanostructured matrix composite was achieved, and (iii) the dendritic β -Ti(M) solid solution acts as a reinforced phase stabilizing the deformation of the nanostructure, so as to achieve a very good balance between high strength and large plasticity of the alloys, indicating that new Ti alloys can be promising candidates as biomedical materials [82]. In addition to these developments, several Ti–Cu series were investigated, including Ti–10Cu–5Pd [83] and Ti–Cu(2–5 w/o)–Si(0.2–2 w/o) [84].

The most frequent complication in external fixation is pin tract infection. To reduce the incidence of implant-associated infection, it is believed to be important to prevent the bacterial adhesion by treating pin surface [85]. Antibacterial activities of Ti–1Cu and Ti–5Cu were evaluated after being exposed to *Staphylococcus aureus* and *Escherichia coli*. It was found that both alloys inhibited colonization by both mentioned bacteria. Cytocompatibility studies were also conducted using fibroblasts and colony formation on both metals by counting the number of colonies, and it was found that Ti–1Cu alloy showed no difference in the number of colonies compared with the CpTi. Furthermore, external fixator pins made of Ti–Cu alloys were evaluated in a rabbit model, and tissue–implant interactions were analyzed for the presence of infection, inflammatory changes, and osteoid formation. It was reported that Ti–1Cu alloy (i) significantly inhibited inflammation and infection and (ii) had excellent osteoid formation. It is concluded that Ti–Cu alloys have antibacterial activity and substantially reduce the incidence of pin tract infection [85].

2.3.11 Ti–Mo

TiMo alloy is widely used as an orthodontic archwire for performing an orthodontic mechanotherapy [86]. When NiTi wire, TMA (β -phase Ti–Mo) wire, and austenitic stainless steel wire were compared, it was found that (i) TMA showed the greatest plastic strain and springback, followed by NiTi and stainless steel, (ii) NiTi wire showed the highest stored energy value in bending torsion, followed by TMA and stainless steel, and (iii) the highest spring ratio (stiffness) in bending torsion was found in stainless steel, followed by TMA and NiTi [87]. Lin et al. [88] studied alloying effect of Fe on the Ti–Mo alloy and found that Ti–Mo with iron

contents in a range from 2 to 5 wt% appeared to have a great potential for use as an implant material.

Electrochemical corrosion resistance of Ti–11Mo–2V–4Nb–3Al was evaluated in Hank's physiological solution through potentiodynamic tests scanning between -0.25 and 3.5 V, and it was reported that the alloy showed a high-corrosion resistance and stabilization of surface after repassivation was established [89]. Among various developed Ti–Mo alloy systems, Ti–15Mo alloys are the most frequently investigated [90–92], due to the facts that the alloys are increasingly utilized for orthopedic implant applications because of their excellent corrosion resistance and low-elastic modulus. Particularly in osteosynthesis, where the biomaterial stands in direct contact with soft tissue, undesirable biologic reactions may have severe consequences, especially in the vulnerable state of trauma and added iatrogenic damage to the microvascular system [90]. Therefore, *in vivo* nutritive perfusion and leukocytic response of striated muscle to the Ti–15Mo with other alloys were assessed. It was concluded that Ti–15Mo induced only a transient inflammatory response of the striated muscles' microvascular system [90]. Oliveira et al. [91] studied *in vivo* bone response, being assessed by removal torque and histological and histometrical analysis on Ti–15Mo alloy, after surface modification by laser beam irradiation. It was reported that average removal torque was 51.5 N cm and bone-to-implant contact (BIC) percentage was significantly higher for laser-treated implants both in the cortical and marrow regions [91]. The role of nanofeatured titanium surfaces in a number of aspects of *in vivo* bone–implant integration and their potential advantages over microfeatured titanium surfaces, as well as their specific contribution to osteoconductivity, is largely unknown [92]. Machined surfaces without microroughness, sandblasted microroughened surfaces, and micro-nano hybrid surfaces created by sandblasted and alkali and heat treatment of Ti–15Mo–5Zr–3Al alloy were prepared for biomechanical, interfacial, and histological analyses in a rat model [92]. It was mentioned that (i) the addition of nanobimorphic features to the microroughened surfaces increased the implant fixation by as much as 60–100% over the healing time, (ii) although the BIC percentage was also significantly increased by the addition of nanobimorphic features, the greatest improvement was found in soft tissue intervention between the bone and the implant, which was reduced from $>30\%$ to $<5\%$. It was, hence, concluded that the nanofeature-enhanced osteoconductivity of titanium by an alkali- and heat-treated nanobimorphic surface compared to that by microfeatured surfaces results not only in the acceleration but also in the improvement of bone–implant integration [92].

2.3.12 Ti–Al Alloys

The beta phase can be introduced to TiAl alloys by the addition of β stabilizing elements such as Cr, Nb, W, and Mo. The β phase has BCC lattice structure and is softer than α_2 and γ phases in TiAl alloys at elevated temperatures and hence is thought to have a detrimental effect on creep strength [93]. Among various Ti–Al–X alloys, it appears to be that Ti–48Al–2Cr–2Nb is the only one that has been extensively investigated on engineering application in jet engines [94],

replacement for the skeletal framework [95], and bone repair and replacement [96]. The potential of gamma TiAl as a biomaterial was evaluated using an *in vivo* rat model [95]. Sprague–Dawley rats were implanted with gamma TiAl cylinders in the femur and observed for an experimental period for 180 days. It was reported that (i) normal bone growth processes were observed as early as 45 days, (ii) no signs of rejection of the implant was observed, (iii), the bone–metal interface showed signs of tissue growth from original bone to the metal surface, and (iv) the gamma TiAl appears to elicit a normal bone tissue reaction and hence has potential as a metallic implant [95]. Similar study was conducted by Rivera-Denizard et al. [96]. Human fetal osteoblast cells were cultured on the surface of gamma TiAl and Ti–6Al–4V disks with variable surface roughness for both SEM and immunofluorescent analysis to detect the presence of collagen type I and osteonectin, proteins of the bone extracellular matrix. It was found that (i) cell growth/attachment on gamma TiAl was normal compared to that of Ti–6Al–4V, suggesting that gamma TiAl is not toxic to osteoblasts, (ii) the presence of collagen type I and osteonectin was observed on both gamma TiAl and Ti–6Al–4V, indicating that gamma TiAl is biocompatible with the osteoblast cells [96].

Although not ordinary alloys, titanium aluminide-based alloys, including TiAl (γ -phase) and Ti₃Al (α_2 phase), are used for high-temperature applications. The titanium aluminide-based alloys provide an inherently low-density material and exhibit excellent creep-rupture properties [25,97]. TiAl amorphous alloy provides high strength, linear elastic behavior, and the infinite fatigue life necessary for high-device reliability. Tregilgas [98] developed amorphatized TiAl alloys for a material for the digital micromirror device chip. In order to enhance the wear resistance of γ -TiAl (Ti–47Al–2Nb) alloy, the surface of this alloy was modified in a nitrogen-ion plasma atmosphere [99].

2.3.13 Other Ti-Based Alloys

Ti–Ta Alloy Systems

An interesting study was done by Brème et al. [100] using isoelectric porous sintered Ti–30Ta alloy and titanium wire loop to accomplish the mechanical compatibility in endosseous dental implant systems. Their mechanical properties were optimized by the production parameter such as sintering and DB. The functionality was tested after insertion into an artificial jaw which had properties corresponding to the natural mandibular. It was reported that the elastic properties of both implants are similar to the properties of the bone, and the implant has a safe anchorage bone ingrowth [100]. Texture evolution in Ti–25Ta–25Nb (β -type) by severe plastic deformation was investigated [101]. Ti oxide nanotubes were formed on the Ti–35Ta–(3–15)Zr alloys by anodizing in H₃PO₄ containing 0.8 wt% NaF solution at 25°C [102]. It was reported that (i) microstructures of the Ti–35Ta alloys were changed from β -phase to α_2 -phase with increasing Zr content, (ii) nanotubular Ti oxide surface and layers consisting of highly ordered nanotubes with a wide range of diameters (approximately 150–200 nm) and lengths

(ca. 4–10 μm) can be formed on Ti–35Nb alloy with Zr contents, and (iii) the nanotubes formed on alloy surfaces were amorphous structure before heat treatment, but the oxide surface had mainly an anatase structure after heat treatment [102].

Ti–Zr Alloy Systems

Ti–Zr alloys show significantly better mechanical attributes than pure titanium with respect to elongation and fatigue strength [103]. Removal torque and histological evaluations were conducted on Ti–(13–17%)Zr alloys and found that the Ti–Zr alloy implant with a hydrophilic sandblasted, and acid-etched surface showed similar or even stronger bone tissue responses than the CpTi control implant [103]. The relationship between the various deformation-induced products and the mechanical properties (elastic modulus, microstructure, and tensile properties) of Ti–30Zr–(5,6,7 mass%) Mo alloys was studied [104]. It was reported that the decrease in elastic modulus due to cold rolling is related to the deformation-induced α' -phase transformation accompanying the disappearance of the athermal ω phase.

Three new Ti alloys (Ti–20Zr–3Nb–3Ta–0.2Pd–1In, Ti–20Zr–3Nb–3Ta–0.2Pd, Ti–15Zr–3Nb–3Ta–0.2Pd) with Zr, Nb, Ta, Pd, and In as alloying elements were developed and compared with currently used implant metals, namely CpTi and Ti–6Al–4V, in terms of mechanical and corrosion properties and cytotoxicity. It was shown that (i) new alloys exhibited comparable mechanical properties with that of Ti–6Al–4V, (ii) there were no significant differences in L-929 cell growth on the surface of the various metal specimens, indicating that the cells cannot differentiate between the passivated surfaces of the various Ti metals, and (iii) after regression analysis, among five alloying elements, Ta was the most effective in improving corrosion resistance, hot workability, and preventing the brittle phase formation [105]. It was reported that Ti–30Zr [106] and Ti–30Hf [107,108] improved mechanical properties as well as machinability.

Ti–Cr Alloy Systems

Problems such as implant fracture and tarnish of the denture base have been on the rise due to their increased use in clinical applications. One cause of these problems is related to the presence of fluoride ion toothpaste [109,110], mouth rinses, and prophylactic agents, which are used to help prevent dental caries. Takemoto et al. [111] investigated the correlation between corrosion resistance and surface composition of an experimental Ti–20Cr casting alloy in saline solution fluoride. The alloy had a greater resistance to corrosion in fluoride-containing saline solution than did CpTi. However, confirmed dissolution of titanium and chromium meant that the fluoride in the saline solution corroded the alloy slightly. It was reported that (i) the $[\text{Ti}]/([\text{Ti}] + [\text{Cr}])$ ratio in the surface oxide film decreased when immersed in fluoride-containing saline solution; that is, the surface oxide film became Cr-rich oxide and (ii) the alloy obtained good corrosion resistance to fluoride due to formation of a chromium-rich oxide film [111].

Mechanical properties [112] and corrosion behaviors [113] of Ti–(5–20 mass %)Cr alloys were investigated and it was reported that (i) addition of 15 or 20 mass % Cr to Ti yielded sufficient strength and relatively high-elongation values and (ii) concentration of chromic species such as oxide and hydroxide in the surface oxide film was associated with Cr content, and chromic species improved the corrosion resistance to fluoride.

Wu et al. [114] evaluated the bond strengths between experimental Ti–20Cr–1X (X: Nb,Mo,Fe,Zr) alloys and porcelain. It was reported that (i) all the Ti–20Cr–1X alloys exceed the lower limit value of 25 MPa (per ISO 9693 standard 3-point bending test), (ii) the coefficient of thermal expansion values are higher than that of CpTi, and (iii) Ti–20Cr–1Mo alloy had a significantly higher bond strength than others due to the closer match in thermal coefficient with porcelain.

Ti–Ag Alloy Systems

Zhang et al. [115] characterized microstructures of Ti–5Ag alloy with and without thermal oxidation treatment and reported that, compared to CpTi, Ti–5Ag alloy without thermal oxidation treatment possesses much lower current density, higher open circuit potential, and larger impedance value, and its corrosion resistance could be further improved with thermal oxidation. Elastic moduli [79], machinability [116], and electrochemical behavior in 0.9% NaCl and 1% lactic acid solutions [117,118] of Ti–(5–40 mass%)Ag alloys were studied and reported that (i) by increasing Ag content, elastic moduli showed the lowest value by 20% and were then increased by increasing Ag content, (ii) values of the component of the horizontal cutting force perpendicular to the feed direction for Ti–20Ag and Ti–30Ag were more than 20% lower than those for Ti under both cutting conditions and alloying with silver significantly improved the machinability of titanium, and (iii) Ti–Ag alloys up to 17.5% Ag had excellent corrosion resistance similar to that of pure titanium. It was therefore suggested that the alloys with 20–25% Ag may be also used as dental alloys, since they passivated again immediately after preferential dissolution in the NaCl solution.

Ti–Fe Alloy Systems

Ti–Fe–Zr alloy samples were produced by die compaction of mixed elemental powders with subsequent densification by sintering 1275°C in vacuum through P/M technology. It was reported that the best property combination was obtained with the addition of 5 wt% Fe and 5 wt% Zr when vacuum sintered at 1275°C for 60 min [119].

Ti–X–B Alloy Systems

Small additions of boron to conventional titanium alloys have been found to produce significant changes to the microstructures and associated properties. Grain refinement and improved strength and stiffness are first-order effects, which lead to

possibilities for developing novel and affordable processing methodologies and to enhance performance over conventional titanium alloys. Boron is completely soluble in the liquid phase of titanium but is essentially insoluble in the solid titanium phases (high-temperature beta or room temperature alpha). Hence, boron added to titanium precipitates in the form of intermetallic TiB phase for additions below 14 wt% (40 at.%). The TiB phase offers unique advantages. The density of TiB is comparable to that of titanium, but the stiffness is about five times greater. Therefore, TiB phase provides significant increases in strength and stiffness without increasing density [120].

References

- [1] Long M, Rack HJ. Titanium alloys in total joint replacement—a materials science perspective. *Biomaterials* 1998;19:1621–39.
- [2] Collings EW. The physical metallurgy of titanium alloys. Cleveland, OH: The American Society for Metals (ASM); 1984. pp. 3–5
- [3] Froes FH. The better characterization of titanium alloys. *J Met* 2005;57:41.
- [4] Hartman AD, Gerdeman SJ, Hansen JS. Producing low-cost titanium for automotive applications. *J Met* 1998;50:16–9.
- [5] van Vuuren DS, Engelbrecht AD, Hadley TD. Opportunities in the Electrowinning of molten titanium from titanium dioxide. *J Met* 2005;57:53–5.
- [6] Fuwa A, Takaya S. Producing titanium by reducing TiCl_4 – MgCl_2 mixed salt with magnesium in the molten state. *J Met* 2005;57:56–60.
- [7] Ivansishin OM, Markovsky PE. Enhancing the mechanical properties of titanium alloys with rapid heat treatment. *J Met* 1996;48:48–52.
- [8] Eylon D, Vassel A, Combres Y, Boyer RR, Bania PJ, Schutz RW. Issues in the development of beta titanium alloys. *J Met* 1994;46:14–5.
- [9] Bania PJ. Beta titanium alloys and their role in the titanium industry. *J Met* 1994;46:16–9.
- [10] Schutz RW. Environmental behavior of beta titanium alloys. *J Met* 1994;46:24–9.
- [11] Kim Y-W. Ordered intermetallic alloys: Part III: gamma titanium aluminides. *J Met* 1994;46:30–9.
- [12] Lopez MF, Gutierrez A, Jiménez JA. In vitro corrosion behavior of titanium alloys without vanadium. *Electrochim Acta* 2002;47:1359–64.
- [13] Metikos M, Kwok A. The influence of niobium and vanadium on passivity of titanium-based implants in physiological solution. *Biomaterials* 2003;24:3765–75.
- [14] Khan MA, Williams RL, Williams DF. The corrosion behavior of Ti–6Al–4V, Ti–6Al–7Nb and Ti–13Nb–13Zr in protein solutions. *Biomaterials* 1999;20:631–7.
- [15] Eylon D, Vassel A, Combres Y, Boyer RR, Bania PJ, Schutz RW. Issues in the development of beta titanium alloys. *J Met* 1994;46:14–5.
- [16] Niiomi M. Recent metallic materials for biomedical applications. *TMS Metall Mater Trans* 2002;33A:477–86.
- [17] Jha SK, Ravichandran KS. High-cycle fatigue resistance in beta-titanium alloys. *J Met* 2000;52:30–5.
- [18] Qazi JI, Marquardt B, Rack HJ. High-strength metastable beta-titanium alloys for biomedical applications. *J Met* 2004;56:49–51.

-
- [19] Niiomi M. Fatigue performance and cyto-toxicity of low rigidity titanium alloy, Ti–29Nb–13Ta–4.6Zr. *Biomaterials* 2003;24:2673–83.
 - [20] Niiomi M, Kuroda D, Fukunaga K, Morinaga M, Kato Y, Yashiro T, et al. Corrosion wear fracture of new β type biomedical titanium alloys. *Mater Sci Eng A* 1999; A263:193–9.
 - [21] ASTM designation F2066-01. Standard specification for wrought titanium-15 molybdenum alloy for surgical implant applications. Philadelphia, PA: American Society for Testing and Materials; 2001. pp. 1605–1608
 - [22] ASTM designation draft #3. Standard specification for wrought titanium–35Niobium–7Zirconium–5Tantalum alloy for surgical implant applications (UNS R58350). Philadelphia, PA: American Society for Testing and Materials; 2000.
 - [23] ASTM designation draft #6. Standard specification for wrought titanium–3Aluminum–2.5Vanadium alloy for surgical implant applications (UNS R58350). Philadelphia, PA: American Society for Testing and Materials; 2000.
 - [24] Paton NE, Williams JC. Effect of hydrogen on titanium and its alloys. In: American Society for Metals. *Hydrogen in Metals*; 1974. pp. 409–32.
 - [25] Donachie MJ, editor. *Titanium and Titanium Alloys—Source Book*. Metals Park, OH: American Society for Metals; 1982.
 - [26] Mountford Jr. JA. Titanium alloys for the CPI (chemical process industry). *Adv Mater Process* 2001;159:55–8.
 - [27] Hernandez FE. Corrosion behavior for commercially pure titanium with different grades and from different material suppliers. Indiana University Master Degree Thesis; 2003.
 - [28] Lim WC. Comparison of electrochemical corrosion behavior among four grades of commercially pure titanium. Indiana University Master Degree Thesis; 2001.
 - [29] Binon PP. Implants and components: entering the new millennium. *Int J Oral Maxillofac Implants* 2000;15:76–94.
 - [30] McCracken M. Dental implant materials: commercially pure titanium and titanium alloys. *J Prosthodont* 1999;8:40–3.
 - [31] Moore BK, Oshida Y. Materials science and technology in dentistry. In: Wise DL, Trantolo DJ, Altobelli DE, Yaszemski MJ, Gresser JD, Schwartz ER, editors. *Encyclopedic handbook of biomaterials and bioengineering*. New York: Marcel Dekker; 1995. pp. 1325–430 [chapter 48].
 - [32] Hefti LD. Fine-grain titanium 6Al–4V for superplastic forming and diffusion bonding of aerospace products. *J Met* 2010;62:42–5.
 - [33] Iijima D, Yoneyama T, Doi H, Hamanaka N, Kurosaki N. Wear properties of Ti and Ti–6Al–7Nb castings for dental prostheses. *Biomaterials* 2003;24:1519–24.
 - [34] Soma H. Clinical application of Ti–6Al–7Nb alloy “Ti-Alloy Tough”. *Quint Dent Technol* 1998;23:98–104.
 - [35] Semlitsch MF, Weber H, Streicher RM, Schoen R. Joint replacement components made of hot-forged and surface-treated Ti–6Al–7Nb alloy. *Biomaterials* 1992;13:781–8.
 - [36] Suzuki T, Takahashi H, Arksornnukit M, Oda N, Hirano S. Bonding properties of heat-polymerized denture base resin to Ti–6Al–7Nb alloy. *Dent Mater J* 2005;24:530–5.
 - [37] Tuominen S, Wojcik C. Alloys for aerospace. *Adv Mater Process* 1993;147:23–6.
 - [38] Higo Y, Ouchi C, Tomita Y, Murota K, Sugiyama H. Properties evaluation and its application to artificial hip joint of newly developed titanium alloy for biomaterials. *Proceedings of the third Japan international SAMPE symposium*; 1993. pp. 1621–25.

- [39] Zwicker U, Brème J. Investigations of the friction behavior of oxidized Ti–5% Al–2.5%Fe surface layers on implant material. *J Less-Common Met* 1984;100:371–5.
- [40] Ouchi C, Minakawa K, Takahashi K, Ogawa A, Ishikawa M. Development of β -rich α - β titanium alloy: SP-700. *NKK Tech Rev* 1992;65:61–7.
- [41] Buehler WJ, Gilfrich JV, Wiley KC. Superelasticity in TiNi alloy. *J Appl Phys* 1963;34:1467–9.
- [42] Duerig TW, Melton KN, Stöckel D, Wayman CM, editors. Engineering aspects of shape memory alloys. London: Butterworth–Heinemann; 1990.
- [43] Civjan S, Huget EF, DeSimon LB. Potential applications of certain nickel–titanium (Nitinol) alloys. *J Dent Res* 1975;54:89–96.
- [44] Bensmann G, Baumgart F, Haasters J. Osteosyntheseklammern aus NiTi. Herstellung, Vorversuche und klinischer Einsatz *Tech Mitt Krupp, Forsch-Ber* 1982;40:123–34.
- [45] Miura F, Mogi M, Ohura Y, Hamanaka H. The superelastic property of the Japanese NiTi alloy wire for use in orthodontics. *Am J Orthod Dentofacial Orthop* 1986;90:1–10.
- [46] Yoneyama T, Doi H, Hamanaka H, Okamoto Y, Mogi M, Miura F. Super-elasticity and thermal behavior of Ni–Ti alloy orthodontic arch wires. *Dent Mater J* 1992;11:1–10.
- [47] Yoneyama T, Doi H, Hamanaka H. Bending properties and transformation temperatures of heat treated Ni–Ti alloy wire for orthodontic appliances. *J Biomed Mater Res* 1993;27:399–402.
- [48] Iijima M, Endo K, Ohno H, Mizoguchi I. Effect of Cr and Cu addition on corrosion behavior of Ni–Ti alloys. *Dent Mater J* 1998;17:31–40.
- [49] Bourauli C, Scharold W, Jäger A, Eliades T. Fatigue failure of as-received and retrieved NiTi orthodontic archwires. *Dent Mater* 2008;24:1095–101.
- [50] Huang HH. Variation in surface topography of different NiTi orthodontic archwires in various commercial fluoride-containing environments. *Dent Mater* 2007;23:24–33.
- [51] Pun DK, Berzins DW. Corrosion behavior of shape memory, superelastic and non-superelastic nickel–titanium-based orthodontic wires at various temperatures. *Dent Mater* 2008;24:221–7.
- [52] Wang J, Li N, Rao G, Han EH, Ke W. Stress corrosion cracking of NiTi in artificial saliva. *Dent Mater* 2007;23:133–7.
- [53] Iijima M, Brantley WA, Guo WH, Clark WAT, Yuasa T, Mizoguchi I. X-ray diffraction study of low-temperature phase transformation in nickel–titanium orthodontic wires. *Dent Mater* 2008;24:1454–60.
- [54] Berzins DW, Roberts HW. Phase transformation changes in thermocycles nickel–titanium orthodontic wires. *Dent Mater* 2010;26:666–74.
- [55] Iijima M, Ohta M, Brantley WA, Naganishi A, Murakami T, Muguruma T, et al. Transformation behavior of nickel–titanium orthodontic wires under tensile load. *Dent Mater J* 2011;30:398–403.
- [56] Alapati SB, Brantley WA, Iijima M, Schricker SR, Nusstein JM, Li UM, et al. Micro-XRD and temperature-modulated DSC investigation of nickel-titanium rotary endodontic instruments. *Dent Mater* 2009;25:1221–9.
- [57] Li UM, Shin CS, Lan WH, Lin CP. Application of nondestructive testing in cyclic fatigue evaluation of endodontic Ni–Ti rotary instruments. *Dent Mater J* 2006;25:247–52.
- [58] Cheung GSP, Darvell BW. Low-cycle fatigue of rotary NiTi endodontic instrument in hypochloride solution. *Dent Mater* 2008;24:753–9.
- [59] Jamleh A, Kobayashi C, Yahata Y, Ebihara A, Suda H. Deflecting load of nickel titanium rotary instruments during cyclic fatigue. *Dent Mater J* 2012;31:389–93.

- [60] Pautke C, Kolk A, Brokate M, Wehrstedt JC, Kneissl F, Miethke T, et al. Development of novel impant abutment using the shape memory alloy: preliminary results. *Int J Oral Maxillofac Implants* 2009;24:477–83.
- [61] Peña J, Solano E, Mendoza A, Casals J, Planell JA, Gil FJ. Effect of the M_s transformation temperature on the wear behavior of NiTi shape memory alloys for articular prosthesis. *Biomed Mater Eng* 2005;15:289–93.
- [62] Domingo S, Puértolas S, Gracia-Villa L, Mainar M, Usón J, Puértolas JA. Design, manufacture and evaluation of a NiTi stent for colon construction. *Biomed Mater Eng* 2005;15:357–65.
- [63] Shabalovskaya S, Anderegg J, Rondelli G, Vanderlinden W, De Feyter S. Comparative in vitro performance of bare Nitinol surfaces. *Biomed Mater Eng* 2008;18:1–14.
- [64] Liu X, Wu S, Yeung KW, Chan YL, Hu T, Xu Z, et al. Relationship between osseointegration and superelastic biomechanics in porous NiTi scaffolds. *Biomaterials* 2011;32:330–8.
- [65] Yahia LH, Manceur A, Chaffraix P. Bioperformance of shape memory alloy single crystals. *Biomed Mater Eng* 2006;16:101–18.
- [66] Katakura N, Takada Y, Iijima K, Hosotani M, Honma H. Studies in the shape memory alloys for biomaterials (Part II)—electrochemical behavior of Ti, Pd, Co and TiPd alloys. *J Jpn Dent Mater* 1991;10:809–13.
- [67] Sohmura T, Kimura HT. Shape recovery in Ti-V-Fe-Al alloy and its application to dental implant. *Proc int conference on martensitic transformation ICOMAT-86. Jpn Inst Metals*; 1987. pp. 1065–70.
- [68] Iijima M, Brantley WA, Baba N, Alapati SB, Yuasa T, Ohno H, et al. Micro-XRD study of beta-titanium wires and infrared soldered joints. *Dent Mater* 2007;23:1051–6.
- [69] Brantley WA, Guo W, Clark WAT, Iijima M. Microstructural studies of 35°C Copper Ni–Ti orthodontic wire and TEM confirmation of low-temperature martensite transformation. *Dent Mater* 2008;24:204–10.
- [70] Setcos J, Babaei-Mahani A, Di Silvio L, Mjör IA, Wilson NHF. The safety of nickel containing dental alloys. *Dent Mater* 2006;22:1163–8.
- [71] Hosoki M, Bando E, Asaoka K, Takeuchi H, Nishigawa K. Assessment of allergic hypersensitivity to dental materials. *Biomed Mater Eng* 2009;19:53–61.
- [72] Kanetaka H, Shimizu Y, Hosoda H, Tomizuka R, Suzuki A, Urayama S, et al. Orthodontic tooth movement in rats using Ni-free Ti-based shape memory alloy wire. *Mater Trans* 2007;48:367–72.
- [73] Müller FA, Bottino MC, Müller L, Henriques VAR, Lohbauer U, Bressiani AHA, et al. In vitro apatite formation on chemically treated (P/M) Ti–13Nb–13Zr. *Dent Mater* 2008;24:50–6.
- [74] Xiong JY, Li YC, Hodgson PD, Wen CE. Design of anew biocompatible Ti-based shape memory alloy and its superelastic deformation behavior. *Mater Sci Forum* 2010;654:2087–90.
- [75] Shimojo N, Kondo C, Yamashita K, Hoshino T, Hayakawa T. Cytotoxicity analysis of a novel titanium alloy in vitro: adhesion, spreading, and proliferation of human gingival fibroblasts. *Biomed Mater Eng* 2007;17:127–35.
- [76] Zhu Y, Wang L, Wang M, Liu Z, Qin J, Zhang D, et al. Superelastic and shape memory properties of $Ti_{4-x}Nb_3Zr_2Ta$ alloys. *J Mech Behav Biomed Mater* 2012;12:151–9.
- [77] Zorn G, Gotman I, Gutmanas EY, Adachi R, Sukenik CN. Surface modification of Ti45Nb alloy by immobilization of RGD peptide via self assembled monolayer. *J Mater Sci Mater Med* 2007;18:1309–15.

- [78] Bhola SM, Bhola R, Mishra B, Olson DL. Povidone-iodine as a corrosion inhibitor towards a low modulus beta Ti–45Nb implant in a simulated body fluid. *J Mater Sci Mater Med* 2011;22:773–9.
- [79] Kikuchi M, Takahashi M, Okuno O. Elastic moduli of cast Ti–Au, Ti–Ag, and Ti–Cu alloys. *Dent Mater* 2006;22:641–6.
- [80] Kikuchi M, Takada Y, Kiyosue S, Yoda M, Woldu M, Cai Z, et al. Mechanical properties and microstructures of cast Ti–Cu alloy. *Biomaterials* 2003;19:174–81.
- [81] Takada Y, Okuno O. Corrosion characteristics of α -Ti and Ti₂Cu composing Ti–Cu alloys. *Dent Mater J* 2005;24:610–6.
- [82] He G, Eckert J, Dai QL, Sui ML, Löser W, Hagiwara M, et al. Nanostructured Ti-based multi-component alloys with potential for biomedical applications. *Biomaterials* 2003;24:5115–20.
- [83] Hattori M, Takemoto M, Yoshinari M, Kawada E, Oda U. Alloying effect of Pd to Ti–Cu alloy. *Proc ninth meeting, soc titanium alloys in dentistry, Tokyo; June 2005*. p. 45.
- [84] Koike M., Okabe T. Mechanical properties of Ti–Cu–Si alloys. *Proc ninth meeting, soc titanium alloys in dentistry, Tokyo; June 2005*. p. 44.
- [85] Shirai T, Tsuchiya H, Shimizu T, Ohtani K, Zen Y, Tomita K. Prevention of pin tract infection with titanium–copper alloys. *J Biomed Mater Res B Appl Biomater* 2009;91:373–80.
- [86] Ho WF, Ju CP, Chern Lin JH. Structure and properties of cast binary Ti–Mo alloys. *Biomaterials* 1999;20:2115–22.
- [87] Drake SR, Wayne DM, Powers JM, Asgar K. Mechanical properties of orthodontic wires in tension, bending, and torsion. *Am J Orthod* 1982;82:206–10.
- [88] Lin DJ, Chern Lin JH, Ju CP. Structure and properties of Ti–7.5Mo–xFe alloys. *Biomaterials* 2002;23:1723–30.
- [89] Martin E, Manceur A, Polizu S, Savadogo O, Wu MH, Yahi LH. Corrosion behavior of a beta-titanium alloy. *Biomed Mater Eng* 2006;16:171–82.
- [90] Pennekamp PH, Wimmer MA, Eschbach L, Burian B, Koch P, Kraft CN. Microvasculatory reaction of skeletal muscle to Ti–15Mo in comparison to well-established titanium alloys. *J Mater Sci Mater Med* 2007;18:2053–60.
- [91] Oliveira NT, Guastaldi FP, Perrotti V, Hochuli-Vieira E, Guastaldi AC, Piattelli A, et al. Biomedical Ti–Mo alloys with surface machined and modified by laser beam: biomechanical, histological, and histometric analysis in rabbits. *Clin Implant Dent Relat Res* 2011;May [Abstract only].
- [92] Tsukimura N, Ueno T, Iwasa F, Minamikawa H, Sugita Y, Ishizaki K, et al. Bone integration capability of alkali- and heat-treated nanobimorphic Ti–15Mo–5Zr–3Al. *Acta Biomater* 2011;7:4267–77.
- [93] Zhu H, Seo DY, Maruyama K. Strengthening behavior of beta phase in lamellar microstructure of TiAl alloys. *J Met* 2010;62:64–9.
- [94] Bartolotta P, Barrett J, Kelly T, Smashey R. Ti–48Al–2Cr–2Nb in jet engines. *J Met* 1997;49:48–50.
- [95] Castañeda-Muñoz DF, Sundaram PA, Ramírez N. Bone tissue reaction to Ti–48Al–2Cr–2Nb (at%) in a rodent model: a preliminary SEM study. *J Mater Sci Mater Med* 2007;18:1433–8.
- [96] Rivera-Denizard O, Difort-Carlo N, Navas V, Sundaram PA. Biocompatibility studies of human fetal osteoblast cells cultured on gamma titanium aluminide. *J Mater Sci Mater Med* 2008;19:153–8.

- [97] Jha SK, Larsen JM, Rosenberger AH. The role of competing mechanisms in the fatigue-life variability of a titanium and gamma-TiAl alloy. *J Metals* 2005;57:50–4.
- [98] Tregilgas J. Amorphous hinge material. *Adv Mater Process* 2005;163:46–9.
- [99] Thongtem S, McNallan M, Thongtem T. Surface modifications of γ -TiAl alloys by nitrogen plasma deposition. *Adv Technol Mater Mater Process* 2004;6:170–5.
- [100] Brème J, Biehl V, Schulte W, D'Hoedt B, Donath K. Development and functionality of isoelastic dental implants of titanium alloys. *Biomaterials* 1993;14:887–92.
- [101] Cojocaru VD, Raducanu D, Gloriant T, Cinca I. Texture evolution in a Ti–Ta–Nb alloy processed by severe plastic deformation. *J Met* 2012;64:572–81.
- [102] Kim EJ, Kim WG, Jeong YH, Choe HC. Nanotubular oxide surface and layer formed on the Ti–35Ta– x Zr alloys for biomaterials. *J Nanosci Nanotechnol* 2011;11:7433–7.
- [103] Gottlow J, Dard M, Kjellson F, Obrecht M, Sennerby L. Evaluation of a new titanium–zirconium dental implant: a biomechanical and histological comparative study in the mini pig. *Clin Implant Dent Relat Res* 2010;June [Abstract only].
- [104] Zhao X, Niiomi M, Nakai M. Relationship between various deformation-induced products and mechanical properties in metastable Ti–30Zr–Mo alloys for biomedical applications. *J Mech Behav Biomed Mater* 2011;4:2009–16.
- [105] Kim T-I, Han J-H, Lee I-S, Lee K-H, Shin M-C, Choi B-B. New titanium alloys for biomaterials: a study of mechanical and corrosion properties and cytotoxicity. *J Biomed Mater Eng* 1997;7:253–63.
- [106] Takahashi S, Kikuchi S, Okuno O. Machinability of Ti–Zr alloy. *Proc ninth meeting, soc titanium alloys in dentistry, Tokyo; June 2005.* p. 58.
- [107] Kikuchi S, Takahashi M, Satoh H, Komatsu S, Okabe T, Okuno O. Machinability of Ti–Hf alloy. *Proc ninth meeting, soc titanium alloys in dentistry, Tokyo; June 2005.* p. 46.
- [108] Satoh H, Kikuchi S, Komatsu S, Okuno O, Okabe T. Mechanical properties of Ti–Hf casts. *Proc ninth meeting, soc titanium alloys in dentistry, Tokyo; June 2005.* p. 57.
- [109] Lausmaa J, Kasemo B, Hansson S. Accelerated oxide grown on titanium implants during autoclaving caused by fluoride contamination. *Biomaterials* 1985;6:23–7.
- [110] Pröbster L, Lin W, Hüttenmann H. Effect of fluoride prophylactic agents on titanium surfaces. *Int J Oral Maxillofac Implants* 1992;7:390–4.
- [111] Takemoto S, Hattori M, Yoshinari M, Kawada E, Asami K, Oda Y. Corrosion behavior and surface characterization of Ti–20Cr alloy in a solution containing fluoride. *Dent Mater J* 2004;23:379–86.
- [112] Hattori M, Takemoto S, Yoshinari M, Kawada E, Oda Y. Effect of chromium content on mechanical properties of casting Ti–Cr alloys. *Dent Mater J* 2010;29:570–4.
- [113] Takemoto S, Hattori M, Yoshinari M, Kawada E, Asami K, Oda Y. Corrosion mechanism of Ti–Cr alloy in solution containing fluoride. *Dent Mater* 2009;25:467–72.
- [114] Wu SC, Ho WF, Lin CW, Kikuchi H, Lin FT, Hsu HC. Surface characterization and bond strengths between Ti–20Cr–1X alloys and low-fusing porcelain. *Dent Mater J* 2011;30:368–73.
- [115] Zhang BB, Wang BL, Li L, Zheng YF. Corrosion behavior of Ti–5Ag alloy with and without thermal oxidation in artificial saliva solution. *Dent Mater* 2011;27:214–20.
- [116] Kikuchi M, Takahashi M, Okuno O. Elastic moduli of cast Ti–Au, Ti–Ag, and Ti–Cu alloys. *Dent Mater* 2006;22:641–6.
- [117] Kikuchi M, Takahashi M, Okuno O. Machinability of experimental Ti–Ag alloys. *Dent Mater J* 2008;27:216–20.

- [118] Takahashi M, Kikuchi M, Takada Y, Okabe T, Okuno O. Electrochemical behavior of cast Ti–Ag alloys. *Dent Mater J* 2006;25:516–23.
- [119] Kadiri HE, Wang L, Gulsoy HO, Suri P, Park SJ. Development of a Ti-based alloy: design and experiment. *J Met* 2009;61:60–6.
- [120] Tamirisakandala S, Miracle DB, Srinivasan R, Gunasekra JS. Titanium alloyed with boron. *Adv Mater Process* 2006;164:41–3.

3 Chemical and Electrochemical Reactions

3.1 Introduction

The intraoral environment is hostile due to corrosive and mechanical actions. It is continuously full of saliva, an aerated aqueous solution of chloride with varying amounts of Na, K, Ca, PO_4 , CO_2 , sulfur compounds, and mucin. The pH value is normally in the range of 6.5–7.5, but under plaque deposits it may be as low as 2.0. Temperatures can vary $\pm 36.5^\circ\text{C}$, and a variety of food and drink concentrations (with pH values ranging pH values from 2.0 to 14.0) stay inside the mouth for short period of time. Loads can go up to 1000 N (normally 200 N as a masticatory force), sometimes in an impact manner. Trapped food debris may decompose, and sulfur compounds cause natural teeth and restorative materials to discolor. Under these chemical and mechanochemical intraoral environments, materials in service in the mouth are still expected to last for relatively long period of time [1].

It is well documented that Ti materials possess an excellent corrosion resistance and form stable and protective oxides, for example Ti materials are one of the best material choices for medical and dental applications. It is inevitable to note that this chapter on corrosion, as well as the following chapter on oxidation, occupies a quite a large portion of this book. What it implies is that environments to which titanium materials have been exposed are still diverse and vary widely in terms of chemical, mechanical, physical, and any combinations of these parameters. In this chapter, we will be reviewing corrosion behaviors of Ti materials when they are exposed to various atmospheres.

It is known that all primitive living species from which *Homo sapiens* originated were created from the ocean, containing about 32–35 m/l of chlorine ion, while the human body contains about 35 mg/l of chlorine ion and saliva has about 5 mg/l of it. Most of the information presented and reviewed in this chapter was obtained from *in vitro* tests, which were conducted in various corrosive media mainly containing chlorine ions. Such media can be divided into four groups: (1) phosphate-buffered artificial saliva, simulating saliva with low chlorine ion concentration (ca., 50 mg/dl Cl^- , that is about 1% NaCl concentration) (2) since internal fluids have a concentration of chlorine ions seven times (35 mg/l of chlorine ion) higher than that of oral fluids (5 mg/l of chlorine ion), simulated body fluid (SBF) with higher ion concentration (350 mg/dl Cl^-), (3) lactic acid, simulating the chemistry of

major constituents of plaque, and (4) dental treatment agents, including whitening agents and fluoride treatment agents. These corrosive media cause discoloration, tarnishing, corrosion, or oxidation of dental materials. Adsorption of biomolecules, regardless of whether it is a consequence of a material being put into service in a biological medium such as a biomedical implant device, is governed by fundamental interactions and surface conditions that are well characterized [2].

3.2 Discoloration

Currently, mouthrinses, toothpaste, dental prophylactic agents containing fluoride, and bleaching treatment agents are popular for esthetic purposes and prevention of plaque and cavity formation. Normally, orthodontic patients are referred to general dentists for fluoride treatments once every 6 months during the course of orthodontic mechanotherapy. Among various bleaching treatments for whitening stained teeth, an overnight (normally for 8 h) bleaching agent containing 10% carbamide peroxide is popular. To achieve a satisfactory outcome, this treatment must be repeated for two consecutive weeks. The corrosive effect of these agents (normally containing fluoride and hydrogen peroxide) on dental metallic materials has not been well documented, although it was reported to decrease the corrosion resistance of titanium in solutions containing fluoride [3–7].

Titanium application in dentistry has steadily increased because of its numerous biocompatibility benefits and mechanical advantages. In orthodontics, titanium is valuable in the treatment of patients with an allergy to nickel and other specific substances [8]. Adell et al. [9] acknowledged the benefits of titanium and how the body responds to it while working on permanent tooth replacements. Due to their biological advantages and excellent corrosion resistance, research and clinical evidence supports the use of unalloyed titanium and its alloys in the body, which consistently remain the first choice for implants in both medical and dental applications.

Such excellent corrosion resistance of Ti materials might be jeopardized when they are in contact with substances containing fluoride. An *in vivo* study by Harzer et al. [8] showed that orthodontic brackets made of titanium show higher plaque accumulation and more discoloration than stainless steel brackets. This was speculated to be due to the morphological alteration of surface layers. When a surface becomes rougher with higher unevenness, the outer surface becomes duller with a discolored appearance. Nonetheless, studies have found that in a fluoridated medium (especially in acid-fluoridated solutions), titanium is degraded [10,11]. Watanabe and Watanabe [12] found that titanium orthodontic appliances with high titanium content (such as unalloyed CpTi—commercially pure titanium) have also shown lower tarnish resistance, especially when immersed in an acidulated phosphate fluoride (APF) solution.

Teeth that have been exposed to a long-term coffee and/or cigarette usage are normally stained. Viral bleaching of such teeth reflects patients' increasing desire

to achieve an optimal esthetic appearance [13–16]. Internal discoloration caused, for example, by tobacco, dentino-genesis imperfecta, or fluorosis, may be removed. Oxygenating agents like carbamide peroxide or hydrogen peroxide H_2O_2 are effectively used for bleaching purposes. Carbamide peroxide is used as a vehicle for transporting H_2O_2 . First, carbamide reacts with uric acid, ammonia, and H_2O_2 . Then, as a second step, H_2O_2 reacts into H_2O and O , which takes electrons from the substance to bleach [14]. The bleaching efficacy is influenced by the application time and the concentration of the effective agent. Such application of the bleaching agents is performed in offices by clinicians (with relatively higher concentration of H_2O_2) or at home by patients themselves (using relatively lower concentration of H_2O_2) [15]. Commercially available bleaching products range from 3% to 9.5% for hydrogen peroxide (which can be converted to a range from 6% to over 19% carbamide peroxide). Although the above discussion is regarding the discolored natural teeth and whitening of such stained teeth, some patients undergoing the nightguard bleaching (e.g., for 8-hour treatment) are likely to have some metallic restorations (i.e., amalgam, crowns made of gold or porcelain fused to a base metal, fixed or removable prosthodontic bridges or partial denture frameworks made of base alloys, and/or titanium implant fixtures). Recently, it was found that exposure of amalgam to common bleaching agents caused an increase in mercury levels in the solutions [17].

The conscientious health-care provider needs to know the consequences of the effects of fluoride agents and bleaching agents on various dental metallic materials intraorally. While it is acknowledged that tarnishing of the metallic dental materials is the visible consequence of these treatments, the implications for biological effects and the structural integrity of the components are unclear. Clinicians need to understand the potentially corrosive nature of the commercially available fluoride and bleaching treatments on intraoral metals, and know when and where to use them [18]. The discoloration efficacy of fluoride treatment agents (2.0% NaF with pH 7.0, 0.4% SnF_2 with pH 7.0, and 1.23% APF with pH 3.5) was tested on Ti–6Al–4V and 17Cr–4Ni PH (Precipitation-Hardening) type stainless steel, and bleaching agents (10% carbamide peroxide) were applied on CpTi (grade II), 70Ni–15Cr–5Mo, type IV gold alloy (70Au–10Ag–15Cu), and Disperalloy amalgam. The degree of discoloration on these treated alloys was examined by a colorimeter and naked eyes. After the baseline measurements of L^* (lightness), a^* (position on the red/green axis), and b^* (position on yellow/blue axis), comparisons were made with the Commission Internationale d’Eclairage (CIE- L^*a^*b) color system, and the value of ΔE^* (defined as the Euclidean distance) can be calculated by $[(L_i - L_f)^2 + (a_i - a_f)^2 + (b_i - b_f)^2]^{1/2}$, where subscripts “i” and “f” indicate the initial value and final value, respectively. It was found that (i) all tested metallic materials exhibit discoloration to various degrees, ranging from 10 to 18 in ΔE^* , (ii) the tooth brushing between each treatment for both fluoride and bleaching treatments indicate a remarkable reduction in the degree of discoloration (i.e., ΔE^* reduced to 2–8) of all tested materials, and (iii) results of naked-eye evaluation performed by three clinicians did not agree well with those in the lower range of ΔE^* , whereas when the discoloration advanced, both evaluations agreed well [18].

When the temperature effect is added to the aforementioned fluoride discoloration, the result will worsen. Ti implants occasionally were strongly discolored after autoclaving, which contains fluorine ions. It is a common procedure to treat endosseous titanium implants with a fluoride solution before they are placed into the bone cavity. This treatment results in a blue discoloration of the titanium surface [19]. The phenomenon was first observed on a titanium box used for storage of titanium implants during autoclaving and surgical procedures [4]. It was found that the oxide film formed on autoclaved Ti implants thickened up to 650 Å (which is about 10 times thicker than on normal implants). Through the microanalyses performed by SIMS (Secondary Ion Mass Spectroscopy), XPS (X-ray Photoelectron Spectroscopy), and ESCA (Electron Spectroscopy for Chemical Analysis), Lausmaa et al. [4] had shown that these oxide films contained considerable amounts of fluorine, alkali metals, and silicon. In the cases where discoloration was observed in clinical situations, the source of fluorine was the textile cloths in which the titanium implant storage box had been wrapped during the autoclaving procedure. The cloths contained residual Na_2SiF_6 , which had been used as an additive to the rinsing water used in the last step of the cloth laundry procedure. Since the biocompatibility of titanium implants is closely related to their surface oxides, it is advisable to avoid all sources of fluorine ions in the implant preparation procedures [4].

Recently, Noguchi et al. [20], studying on CpTi, Ti–0.15Pd, Ti–6Al–4V, Ti–7Nb–6Al, Ti–55Ni, Ti–10Cu, and Ti–20Cr alloys, compared the differences in discoloration and dissolution when being immersed in two corrosion media: (i) 0.2% NaF + 0.9% NaCl (pH 3.8 with lactic acid) and (ii) 0.1 mol/l H_2O_2 + 0.9% NaCl (pH 5.5). Discoloration was determined with a color meter and released elements were measured using ICP–OES system. It was found that, in media (i), color difference was higher in Ti–55Ni and Ti–6Al–4V alloys than in any other alloys, and Ti–55Ni showed the highest extent of dissolution. On the other hand, in media (ii), CpTi, Ti–0.15Pd, Ti–6Al–4V, Ti–7Nb–6Al, and Ti–10Cu alloys showed remarkable discoloration and dissolution. It was further mentioned that Ti–20Cr exhibited very little discoloration and dissolution in both corrosive media [20].

3.3 Corrosion in Media Containing Fluorine Ion and Bleaching Agents

While numerous studies have been carried out on the corrosion of titanium and titanium-based alloys, few have taken into account the influence of fluoride and pH on CpTi [21–29]. Fluorine ion-containing solution can be found mainly as sodium fluoride NaF solution, as seen in the following.

During the orthodontic mechanotherapy, practitioners recommended their patients use a fluoride mouthwashing agent. Fluoride promotes the formation of calcium fluoride globules that adhere to the teeth and stimulate remineralization while protecting against acid attack. Fluoride mouthwashes thus help prevent the

development of cavities and protect dental enamel. Corrosion behaviors of TMA (75.5Ti–14Mo–5.5Sn–5.5Zr), NbTi (52Nb–48Ti), NiTi (55Ni–45Ti), and NiTi–Cu (48Ni–46.5Ti–5.5Cu) were evaluated in the Fusayama–Meyer artificial saliva, and three commercially available mouthwashes containing NaF of 150, 125 ppm amine fluoride and 125 ppm stannous fluoride SnF₂, and 65.9 ppm sodium monofluoro-phosphate (all in pH 4.2–4.5). It was concluded that (i) NiTi alloy showed a strong corrosion in the presence of monofluoro-phosphate, (ii) NbTi alloy exhibited the most resistance to corrosion, and (iii) TMA corroded strongly with the stannous fluoride SnF₂ [30].

Under a combination of materials (CpTi, Ti–6Al–4V, 17-4 PH-type stainless steel, 70Ni–15Cr–5Mo alloy, type IV (70Au–10Ag–15Cu) gold alloy, and Disperalloy dental amalgam) and dental treatment agents (artificial saliva solution, NaF-containing solution, SnF₂-containing solution, APF, and carbamide peroxide solution), electrochemical polarization tests were conducted to evaluate their corrosion resistance [18]. It was found that (i) The V/Al elemental ratios of Ti–6Al–4V brackets were not significantly different between a sound structure (0.526 ± 0.031) and an irregularly attacked structure (0.533 ± 0.026) after treatment in SnF₂-containing agent and APF agents, (ii) with the same treatments as (i), Cr/Fe ratios of 17-4 (17Cr–4Ni–79Fe) stainless steel brackets were significantly different in terms of sound structure (0.246 ± 0.007) and intergranularly damaged structures (0.177 ± 0.003), indicating the 17-4 stainless steel suffered from the localized Cr depletion, (iii) no stable passivation stages were observed on both Ti–6Al–4V alloy and 17-4 stainless steels under the anodic polarization in the APF agents, and (iv) no stable passivation was established with all the tested alloys when polarized in carbamide peroxide solution. Hence, it was concluded that, although fluoride and bleaching treatments are indicated for patients, it was proven that these treatments are contraindicated for dental metallic materials [18,20,31,32]. Yoon et al. [33] tested CpTi, Ti–6Al–4V, and NiTi in 2% NaF electrolyte, containing 1–20 ppm fluorine ion. It was reported that CpTi and Ti–6Al–4V showed similar current density, whereas NiTi had higher current density (meaning less corrosion resistance) than the other two alloys.

Similarly, Matono et al. [34], studying on CpTi, Ti–6Al–7Nb, and Ti–6Al–4V alloys along with the experimentally developed Ti–0.5Pt alloy, evaluated corrosion behaviors in 0.05% and 2.0% concentrations of APF solutions (corresponding to 226–9050 ppm fluoride at pH 3.5–3.6). It was reported that surfaces of Ti–7Nb–6Al and Ti–6Al–4V alloys were entirely covered with compact corrosion products of Na₃TiF₆ as a result of severe corrosion. Titanium ion dissolution was prevented and the amount of titanium ion dissolved decreased.

The corrosion behaviors of CpTi, Ti–6Al–4V, Ti–6Al–7Nb, and the new experimental alloys—Ti–Pt (0.1–2 wt%) and Ti–Pd (0.1–2 wt%)—were investigated using anodic polarization and corrosion potential measurements in an environment containing 0.2% NaF (905 ppm F) adjusted to pH of 4 in H₃PO₄ at 37°C. It was found that, although the surfaces of the Ti–Pt and Ti–Pd alloys were not affected by an acidic environment containing fluoride, the surfaces of the CpTi, Ti–6Al–4V, and Ti–6Al–7Nb were markedly roughened by corrosion, providing

artifact discolored appearance too. It was also reported that (i) the surfaces of CpTi, Ti–6Al–4V, and Ti–6Al–7Nb were microscopically damaged by corrosion when they were immersed in the solution containing a low concentration of dissolved oxygen, even with a fluoride concentration included in the commercial dentifrices and (ii) in this situation, the surfaces of the new Ti–Pt and Ti–Pd alloys were not affected. As a result, it was suggested that Ti–Pt and Ti–Pd alloys are expected to be of use in dental work as new titanium alloys with high corrosion resistance [35].

During the course of the fluoride corrosion process, hydrogen as a reaction product may cause a delayed fracture, similar to a well-known hydrogen embrittlement (HE), which often takes place in high-strength steels. HE of a β titanium orthodontic wire has been examined by means of a delayed-fracture test in acid and neutral fluoride aqueous solutions and hydrogen thermal desorption analysis. It was found that (i) the time to fracture increased with decreasing applied stress in 2.0% and 0.2% APF solutions, (ii) the fracture mode changed from ductile to brittle when the applied stress was lower than 500 MPa in 2.0% APF solution, and (iii) on the other hand, the delayed fracture did not occur within 1000 h in neutral NaF solutions, although general corrosion was also observed to be similar to that in APF solutions. It was also reported that the amount of absorbed hydrogen was 5000–6500 ppm under an applied stress in 2.0% APF solution for 24 h. Based on these findings, it was concluded that immersion in fluoride solutions leads to the degradation of the mechanical properties and HE-related fracture of β titanium alloy associated with hydrogen absorption [36].

Effects of plastic strain on corrosion behaviors have been studied, but there is also a unique study on the effect of even elastic strain on corrosion behavior. The corrosion resistance of CpTi (grade II) in 1% NaCl + 0–1% NaF solution (pH 6) under different elastic tensile strains (0, 1, 2, and 4%) was tested by the EIS¹ (Electrochemical Impedance Spectroscopy) method. The results showed that (i) the NaF concentration and the elastic strain had a significant influence, (ii) the R_p (polarization resistance, which is equivalent to corrosion resistance) decreased on increasing the NaF concentration and elastic tensile strain, (iii) when the NaF concentration was lower than 0.01%, the R_p value ($> 3.4 \times 10^5 \Omega \text{ cm}^2$) was mainly ascribed to the formation of a protective TiO_2 on the metal surface, regardless of applied strain, and (iv) when the NaF was higher than 0.1%, the protectiveness of TiO_2 was destroyed by F ions, leading to severe pitting corrosion of CpTi [39].

¹ The EIS technique is conducted under AC current; hence the results are frequency dependent, whereas the ordinary electrochemical polarization tests are performed under DC current. The physical meaning of AC impedance can be considered equivalent to that of DC resistance. Although the EIS technique was developed initially for evaluating the performance of organic coating/metal systems, recently it has been extensively employed in corrosion science and engineering. Only a few mV is required for application on the test metallic sample surface, so that the sample surface is not altered, while DC corrosion tests apply, in some cases, up to 1.5 V. This extremely low level of voltage is one of the remarkable advantages over the DC method [37,38].

Yamazoe et al. [40], studying on CpTi, Ti–6Al–4V, Ti–6Al–7Nb, Ti–0.5Pt, Ti–6Al–0.5Pt and Ti–6Al–7Nb–0.5Pt, had examined their corrosion behaviors using an electrochemical analyzer in artificial saliva containing 0.1 and 0.2% NaF at pH of 4.0. It was found that in artificial saliva containing 0.1% NaF the amounts of Ti dissolved from CpTi, Ti–6Al–4V and Ti–6Al–7Nb alloys were about 50 times larger than those of the alloy containing 0.5 wt% Pt. In addition to this result, since the tensile strengths of the alloys containing 0.5 wt% Pt were equal to or higher than those of CpTi or alloys without Pt, Pt-containing alloys are expected to be useful in clinical dentistry with high corrosion resistance and mechanical strength [40].

Experimental evidence obtained by EMPA (Electron Probe MicroAnalyzer) analysis indicated that the detected fluorine on the Ti surface immersed in the solution with fluoride was at a high level, while the detection of sodium was relatively low. Therefore, it can be speculated that fluoride-titanium or fluoride-hydrogen compounds were deposited on the Ti surface rather than sodium fluoride. This is supported by suggestions made by Wilhelmsen and Grande [5] and Nakagawa et al. [24]. Based on the above evidence, it was postulated that hydrofluoric acid (HF) respond by destroying the passive film on Ti but not the fluoride ion. At first, NaF is decomposed into a sodium ion and fluoride ion in the solution. The fluoride ion becomes hydrofluoric acid partially depending on the pH of the solution. The HF attacks the passive films on the Ti surface. By knowing the increase in pH value after immersion of Ti in the solution with fluoride, it might be that the HF decomposed to form fluoride ions and protons or water molecules on the titanium surface by the following formulas: $\text{Ti}_2\text{O}_3 + 6\text{HF} \rightarrow 2\text{TiF}_3 + 3\text{H}_2\text{O}$, $\text{TiO}_2 + 4\text{HF} \rightarrow \text{TiF}_4 + 2\text{H}_2\text{O}$, or $\text{TiO}_2 + 2\text{HF} \rightarrow \text{TiOF}_2 + \text{H}_2\text{O}$. Ti fluoride compounds are formed because fluoride ions bound to the Ti or Ti oxide are decomposed and dissolved in the solution. Protons are absorbed by the titanium substrate or dissolved into the solution as water molecules since it is reported that the titanium alloys absorb hydrogen [5,35,36].

When albumin was mixed with fluoride-containing corrosion media, the corrosion behavior was noticed to change remarkably. The corrosion behavior and surface characterization of passive films on titanium immersed in a solution containing 2.0 g/l fluoride and albumin (either 0.1 or 1.0 g/l) were investigated. It was found that (i) fluorine was detected on the titanium surface immersed in the solution containing fluoride and dissolution of the titanium was confirmed, (ii) the titanium immersed in a solution containing both fluoride and albumin had an albumin film regardless of the albumin concentration level, and (iii) in addition, the amount of dissolved titanium from the titanium immersed in the solution was less than when the solution contained no albumin [3]. It was therefore suggested that the formation of adsorbed albumin films on the passive film acted to not only protect the titanium from attack by the fluoride but also suppressed dissolution of the titanium-fluoride compounds.

The corrosion behavior of Ti–15Mo alloy was investigated in 0.15 M NaCl solution containing varying concentrations of fluoride ions (190, 570, 1140, and 9500 ppm) using potentiodynamic polarization, EIS, and chronoamperometric/

current-time transient (CCT) studies to evaluate its suitability for dental implant applications [41]. It was reported that there was a strong dependence of the corrosion resistance on the concentration of fluoride ions in the electrolytes. Increase in fluoride from 0 to 9500 ppm shifts the corrosion potential (E_{CORR}) from -275 to -457 mV versus saturated calomel electrode (SCE), increases the corrosion current density (i_{CORR}) from 0.31 to $2.30 \mu\text{A}/\text{cm}^2$, the passive current density (i_{PASS}) from 0.07 to $7.32 \text{ mA}/\text{cm}^2$, and the double-layer capacitance (C_{DL}) from 9.63×10^{-5} to 1.79×10^{-4} F, and reduces the charge transfer resistance (R_{CT}) from 6.58×10^4 to $6.64 \times 10^3 \Omega \text{ cm}^2$. In spite of the active dissolution, the Ti–15Mo alloy exhibits passivity at anodic potentials at all concentrations of the fluoride ions studied. In dental implants, since the exposure of the alloy will be limited only to its neck portion, the amount of Mo ions released from Ti–15Mo alloy is not likely to show an adverse and hence, in terms of biocompatibility, Ti-based alloy seems to be acceptable for dental implant applications [41].

3.4 Corrosion under Influences of Environmental and Mechanical Actions

Before the corrosion behavior of titanium and its alloys is discussed, intraoral environments need to be reviewed. It is obvious that the mouth is full of saliva, which can be defined as an ocean of ions, nonelectrolytes, amino acids, proteins, carbohydrates, and lipids, which flows into dental surfaces and contains chloride ions and sulfated compounds. Sulfated compounds are easily metabolized into more corrosive agents by microorganisms. In some cases, blood is another aggressor [42]. Internal fluids have a concentration of chloride ions seven times higher than that of oral fluids, as mentioned previously. A diet rich in sodium chloride, added to large volumes of acidulated beverages (phosphoric acid), provides a continuous source of corrosive agents, despite the relatively short exposure. In addition, it has been calculated that an average urban mouth-breather inhales about a cubic meter of air every 2 h, with a potential intake of between 0.11 and 2.3 mg of sulfur dioxide [43]. Both sulfur dioxide and hydrogen sulfide have been found to accelerate tarnishing and corrosion of metal implants.

The pH value of intraoral liquid is everchanging, depending on the age (the saliva pH tends to increase in acidity with age) and the type of food and beverage. The pH of several normal beverages is as follows: milk 6.7 , beer and wine 4.5 , orange juice 3.3 , Diet Coke 3.0 , vinegar 2.1 , lemonade 2.0 ; stomach acid pH is about 2.0 . Even among different animal models, there can be remarkable differences in pH values. For example, the saliva pH of fowl, swine, and dogs is in a range from 6.5 to 7.5 , while the pH of saliva in sheep, cattle, and horses ranges from 7.8 to 8.2 . Therefore, the results using animal models possess a risk of material overestimation when they are used in human saliva since saliva pH in these animal models is less acid than the pH of human saliva. If plaque is built up on

tooth structure, it is basically due to lactic acid, so that the acidity of the plaque is very low (< 3.0).

Besides chlorine ion levels and pH of intraoral fluids [44], there is one more important factor involved in corrosion evaluation, namely intraoral electrochemical potential. Electrochemical corrosion studies are normally performed by means of potentiostatic or potentiodynamic measurements. Interpretation of the electrochemical corrosion data requires knowledge of expected intraoral potentials. Nilner and Holland [45] reported that the intraoral potential ranges from -431 to -127 mV, which were measured on 407 amalgam restorations in the mouths of 28 patients. Corso et al. [46] reported that the intraoral potential is in a range from -300 to $+300$ mV. Reclaru and Meyer [47] reported a range from 0 to $+300$ mV. Ewers and Thornber [48] reported that it ranges between -380 and $+50$ mV. Hence, the range of overlapping data is a very narrow window of potential zone from 0 to $+50$ mV. It is important to estimate the passivity capability of the material concerned in such an oral environment, and such estimation can be performed without conducting any electrochemical corrosion tests. For example, referring to the Pourbaix [E-pH] diagram [49], one can evaluate the passivation stability as well as capability of the material concerned by knowing the reasonable range of pH in saliva (i.e., $5.5-7.5$) and the above-discussed potential (E) range (i.e., $0-50$ mV).

In addition to the above-listed intraoral chemistry and potential, it is important to know how to simulate the intraoral environments when the *in vitro* chemical or electrochemical corrosion test is prepared and conducted. Many studies have been done to measure the corrosion characteristics of implant metals [50]. Most of these studies have been carried out using physiological isotonic electrolyte solutions such as 0.9% saline [51–56], Ringer's [57–61], Tyrode's [62,63], Hank's [64] solutions, or lactic acid to simulate the accumulated plaque [65,66].

Due to differences in the electrolytes used, the corrosion results could be varied. Alkhateeb and Virtanen [67] have investigated the influence of the spontaneous surface modification of titanium by exposure to Ringer's solution at open-circuit conditions on the passive behavior. The electrochemical behavior of Ti was compared in a simple NaCl and in Ringer's physiological solution. Potentiodynamic polarization curves showed significantly higher passive current densities when tested in Ringer's solution as compared with the simple saline solution, indicating that Ringer's solution is a more corrosive agent. Furthermore, impedance spectra measured at the open-circuit potential as a function of time showed that in saline solution, a long-term exposure over some days leads to a strong increase of the protectiveness of the passive film [67]. Hence, the passive film can grow in mild corrosive solution. Microanalytical studies using SEM and XPS showed that the surface of Ti was modified with Ca and P species from Ringer's physiological solution [66].

Although the above-mentioned electrolytes simulate the body fluids by reproducing the concentrations of various salts, the *in vivo* corrosion measurements have indicated lower corrosion rates than those predicted from these *in vitro* experiments. The actual *in vivo* environment is made up of salts and proteins [68,69]. The amount of protein charge is related to the number of amino and carboxyl

groups. The net charge varies with the pH of the environment; they have a neutral charge at their isoelectric point. The principal protein present in extracellular body fluids is albumin, which has an isoelectric point of 4.5 and, therefore, has a negative charge at a neutral pH. It is possible that these charged molecules could in some way interact with the corrosion reactions and account for the differences between *in vitro* and *in vivo* corrosion rates. Several studies have been done in attempting to understand the effect of proteins on corrosion rates. After various metals were implanted in the body, or in simulated body conditions, corrosion products were found in the blood, sweat, urine, hair, and local tissue around the implant [70–72]. In *in vitro* tests, it was found that the serum proteins albumin and fibrinogen were absorbed to different extents on different metals [73]. In some cases, the corrosion rate was increased by the presence of these proteins, causing denaturation of the proteins [74]. Clark and Williams [75] found that pure metals which form stable passive layers, such as Ti and Al, were unaffected by the presence of proteins; however, the corrosion rate of other transition metals with variable valencies was increased, suggesting that this could be due to the ability of these metals to form stable complexes with the proteins. Speck and Fraker [76] looked at the effect of the amino acids cysteine and tryptophan on titanium alloys. They found that the pitting potential of NiTi was adversely affected by cysteine, but Ti–6Al–4V was not affected by both amino acids. Brown and Merritt [77] used weight loss and chemical analysis techniques to study the static dissolution rate of 316L (low carbon containing 18Cr–8Ni–2Mo) stainless steel cylinders to which they applied a 5 V anodic potential relative to a stainless steel counter electrode in 0.9% saline, 1% and 10% newborn calf serum. They found that the presence of serum increased the corrosion rate, and that 10% serum had a greater effect than the 1% serum.

There are normally chemical or electrochemical ways to investigate and evaluate corrosion behavior. By chemical corrosion, the corrosion rate can be calculated by weight change (in terms of weight loss due to dissolution or weight gain due to corrosion products attached). On the other hand, methods of electrochemical thermodynamics (electrode potential-pH equilibrium diagram) and electrochemical kinetics (polarization curves) may help understand and predict the corrosion behavior of metals and alloys in chosen corrosive media. The corrosion rate can be estimated by measuring the R_P (polarization resistance) or directly the corrosion current density, I_{CORR} . It is important to investigate the interface phenomena between the material and environment. To determine the biocompatibility of a biomaterial, it is important to understand the phenomena at the interface between the biomaterial and the biological system into which the material is to be implanted. At such an interface, the molecular constituents of the biological system meet and interact with the molecular constituents of the surface of the biomaterial. Since these interactions occur primarily on the molecular level and in a very narrow interface zone having a width of less than 1 nm, surface properties on the atomic scale, in particular the composition and structure of the surface layer of biomaterials, may play important roles in interfacial phenomena [77,78].

There are several corrosion studies on CpTi and comparison with other materials. The corrosion of pure metals Al, Co, Cu, Cr, Mo, Ni, and Ti and of a

Co–Cr–Mo casting alloy has been studied in buffered saline with and without the presence of the proteins, serums albumin, and fibrinogen. It was found that (i) the corrosion of Al and Ti was unaffected by the protein, (ii) the corrosion rates of Cr and Ni showed a slight increase, while Co and Cu dissolved to a much greater extent in the presence of protein, and (iii) the corrosion of the Mo element, however, was inhibited by protein [74].

Pohrelyuk et al. [79], studying on nitride-coated Ti–6Al–4V alloy, investigated the corrosion resistance in 0.9% NaCl solution at 36°C and 40°C. It was concluded that forming of nitride film improved the anticorrosion characteristics of the alloy regardless of the temperature of the corrosion environment [79].

Mareci et al. [80] stated that Ti–Ta alloys have been developed, and these are expected to become more promising candidates for biomedical and dental applications than conventional titanium materials (including CpTi, Ti–6Al–4V, and Ti–6Al–7Nb). The corrosion behavior of the Ti–Ta alloys (with Ta contents varying from 30, 40, 50, and 60 wt%) by open-circuit potential measurement, linear polarization, potentiodynamic polarization, coulometric zone analysis, and EIS in artificial saliva with different pH, acid lactic, and fluoride contents. (i) A decrease in corrosion resistance and less-protective passive behavior for all the Ti–Ta alloys in fluoridated acidified saliva, and lactic acid was found and (ii) Ti–Ta alloys in all saliva was better than or similar to that of Ti–6Al–7Nb alloy was studied [80].

Biocompatibility is one of the important conditions for biological materials, and since titanium is considered to have a high biological affinity, it is used in dental and/or medical materials. In fact, in patients with hypersensitive reactions to the present dental alloys, pure titanium is one of the metals that can be used for dental restoration. However, there have been several studies describing patients who did not adapt to titanium [81–83] or who were allergic to titanium [84–87]. In the oral cavity, dental plaque, which includes organic acids such as lactic and formic acid, is more likely to precipitate on the titanium surface when compared with other dental metal alloys [88]. The kinds and concentration of organic acids can vary depending on whether the environment is aerobic or anaerobic [89]. Furthermore, the pH around titanium was reduced when in contact with other metals such as amalgam [90] due to the electrogalvanism. The pH of dental plaque after consuming sugar is about 4.0 [91], but it can range from 2.0 to 14.0, depending on the foods and beverages consumed [92]. Based on such a complexity of the intraoral environments, Kasemo and Lausmaa [81] conducted immersion–corrosion tests on cast CpTi (grade II), in 128 mmol/l of lactic acid and formic acid to pH of 1.0, 4.0, 5.5, 7.0, and 8.5 using 1 N HCl or 1 N NaOH. Tests were performed at 37°C for 3 weeks. It was concluded that (i) CpTi dissolved in all lactic acid aqueous solutions, and the amount of dissolved Ti tended to decrease with a higher pH level, (ii) in formic acid, the amount of dissolved Ti at pH 1.0 was larger than that in lactic acid at the same pH but less than the detectable limit at pH 4.0 or higher, (iii) significant discoloration was macroscopically observed only in formic acid at pH 2.5 and 4.0, (iv) the weights of all the Ti samples immersed in lactic acid decreased (indicating the dissolution of the titanium element) but were not affected by pH, and (v) in formic acid, the weight decreased at pH and the

dissolution increased at pH 2.5–5.5 [81]. These results support the evidence that CpTi exhibits excellent corrosion resistance in strong oxidizing agents and in high chloride concentrations [93].

CpTi and nitrided CpTi (with gold-colored TiN, whereas Ti₂N reveals a silver color) were tested in 1.5 M H₂SO₄ at 20°C. The CpTi, when coupled with less precious metals (like stainless steel), was easily subjected to a strong cathodic polarization. It was concluded that (i) 316L stainless steel behaves as a cathode in galvanic couples of freshly prepared samples with freshly prepared CpTi samples and (ii) 316L stainless steel behaves as an anode in galvanic couples when it is coupled with TiN coatings [94] since freshly polished Ti surfaces exhibit chemically more active than the counter electrode 316L stainless steel, which might be covered already with spinel-type oxides (i.e., Fe₃O₄, (Fe,Ni)₂O · (Fe₂O₃), or (Fe,Ni)O · (Fe,Cr)₂O₃) prior to corrosion tests.

Hernandez [95] investigated and compared electrochemical corrosion behaviors of four different CpTi grades (grades I, II, III, and IV), which were obtained from different material suppliers. The tests were performed in 37°C Ringer's solution. It was found that (i) CpTi grade III was the most corrosive in comparison with suppliers and grades and (ii) CpTi grade IV exhibits the best corrosion resistance.

Kuphasuk et al. [96] tested and compared CpTi (grade II), Ti–5Al–2.5Fe, Ti–4.5Al–3V–2Mo–2Fe, Ti–5Al–3Mo–4Zr, Ti–6Al–4V, and NiTi for their corrosion resistances and passivation capabilities in 37°C Ringer's solution (8.6 g NaCl, 0.3 g KCl, 0.33 g CaCl₂ to make 1000 cm³ with distilled water). It was found that (i) all samples showed good resistance to electrochemical corrosion over the potential of relevance to intraoral conditions, (ii) CpTi and Ti–5Al–2.5Fe showed significantly different corrosion properties than Ti–6Al–4V and NiTi; the former pair exhibited the lowest corrosion rate; the latter pair exhibited the highest corrosion rate, and (iii) NiTi alloys revealed transpassive (in other words, breakdown of stable passivation) behavior at the potential between 0.5 and 0.75 V (vs. SCE as a standard electrode, having 0.24 V vs. hydrogen electrode) accompanied by pitting corrosion, and (iv) all samples tested were covered mainly with the rutile type of TiO₂, which was identified by electron transmission diffraction [96].

Güleriüz and Çimenoglu [97] investigated the thermal oxidation for Ti–6Al–4V to determine the optimum oxidation conditions and to evaluate corrosion-wear performance. Corrosion testing was conducted in 5 M HCl solution. The examined Ti–6Al–4V exhibited excellent resistance to corrosion after oxidation at 600°C for 60 h. This oxidation condition achieved 25 times higher wear resistance than the unoxidized alloy during reciprocating wear testing in 0.9% NaCl solution [97]. Although it was reported in this study that preoxidation of Ti–6Al–4V at 600°C improved the wear corrosion resistance, the oxidation duration of 60 h is questionable. According to the author's experiments, such prolonged oxidation of Ti–6Al–4V should result in too thick of an oxide layer (not film) of grayish-white TiO₂. Such a thick oxide layer does not adhere firmly to the substrate surface but rather tends to peel off from it.

As seen in the following, there are numerous studies on the corrosion behavior of NiTi materials. One reason for this is the fact that almost half of the atomic

percentage of this alloy is Ni, which is considered to be one of the three heavy toxic elements along with Cr and V, and therefore the safety and biocompatibility should be examined thoroughly. Over the last decade, due to its unique shape memory effect (SME) and superelastic (SE) characteristics, NiTi alloys have been increasingly considered for use in external and internal biomedical devices, for example, orthodontic wires, endodontic files, blade-type dental implants, self-expanding cardiovascular and urological stents, bone fracture fixation plates, and nails. For application in the human body, the corrosion resistance of NiTi becomes extremely important, as the amount and toxicity of corrosion products control the alloy biocompatibility. NiTi (with 55.6 w% of Ni) was coated with the powder immersion reaction-assisted nitridation (TiN), followed by annealing at 900°C and 1000°C. Samples were corrosion tested in a solution (9.00 g/l NaCl, 0.20 g/l NaHCO₃, 0.25 g/l CaCl₂ · 6H₂O, 0.4 g/l KCl) at 37°C. It was concluded that (i) the modified NiTi surface consisted of thin outer layer of gold-colored titanium nitride (TiN) and thicker Ti₂Ni layer underneath, (ii) untreated NiTi was found susceptible to pitting corrosion, and (iii) the nitriding treatment improved the corrosion resistance of NiTi [98].

Huang [99] evaluated the corrosion resistance of stressed NiTi and stainless steel orthodontic wires using cyclic potentiodynamic and potentiostatic tests in acid artificial saliva at 37°C. An atomic force microscope was used to measure the 3-D surface topography of as-received wires. It was found that (i) the cyclic potentiodynamic test results showed that the pH had a significant influence on the corrosion parameters of the stressed NiTi and stainless steel wires, (ii) the pitting potential, protection potential, and passive range of stressed NiTi and stainless steel wires decreased by increasing acidity, whereas the passive current density increased by decreasing pH, (iii) the load had no significant influence on the above corrosion parameters, and (iv) for all the pH and load conditions, the stainless steel wire showed higher pitting potential and wider passive range than the NiTi wire, whereas the NiTi wire had lower passive current density than the stainless steel wire [99]. This suggests that NiTi can be passivated easier than stainless steel. As seen previously, it was reported that even elastic strain caused titanium materials to be more corrosive under the presence of fluorine ion [37], suggesting that this study [99] and a previous study [37] do not agree well with each other. The fluorine ion must be very corrosive substance.

The breakdown potentials (for passivation) were measured for unpolished and mechanically polished NiTi wires in SBFs. It was reported that (i) significantly higher passivation breakdown potentials (which indicate a higher stability of passive film formed on NiTi surface) were observed for cross-section wire samples and (ii) some wires were tested in human blood and the passivation breakdown values were higher than that measured in Ringer's and 0.9% NaCl solutions. It was also reported that the oxide film formed on NiTi was predominantly made up of TiO₂ with a very thin layer of NiO at the outer surface. Carroll and Kelly [100] furthermore conducted the galvanic corrosion tests on NiTi wires which were coupled with gold, elgiloy/phynox, and stainless steel. NiTi was found to be anodic in all combinations. In tests in which NiTi–gold couples were immersed in 0.9% NaCl

for periods of up to 12 months, only very small amounts of nickel (in the parts per billion range) were detected [100], indicating that TiO_2 with trace amounts of NiO protects the substrate material well.

Similar studies, which were performed using a cyclic potentiodynamic test in artificial saliva with various acidities, were done on as-received commercial NiTi dental orthodontic archwires from different manufacturers by Huang [101]. The results showed that the surface structure of the passive film on the tested NiTi wires were identical, containing mainly TiO_2 , with small amounts of NiO. The corrosion tests showed that both the wire manufacturer and solution pH had a statistically significant influence on the corrosion potential, corrosion rate, passive current, passivation breakdown potential, and crevice-corrosion susceptibility [101]. It is well known that different orthodontic wire manufacturers employ their own proprietary techniques for wire drawing into the final specified dimensions, resulting in varying surface cleanness as well as roughness.

Hence, from the above, the good corrosion resistance of NiTi may result from the formation of stable, continuous, highly adherent, and protective oxide films on its surface. In fact, due to the high chemical activity of the Ti surface, a damaged oxide film can generally heal itself if at least traces of oxygen or water (moisture) are present in the environment [102,103]. In addition, calcium-phosphate surface films can be naturally formed on Ti alloys in a biological environment [66,104,105], which can act as a further barrier against ion diffusion from the sub-surface alloy. Indeed any surface treatments of NiTi devices have a critical influence on biocompatibility. Two methods have been considered for improving the corrosion resistance and performance of an additional surface barrier layer against ion diffusion, such as TiN, TiC, and TiB_2 ; one method is implantation with diffusion species [106–108] and the other relies on increasing the thickness of the oxide layer by anodizing, thermal oxidation, or implantation with oxygen [109,110]. NiTi was evaluated in Hank's solution (KCl 400 mg/l, KH_2PO_4 60 mg/l, Na_2HPO_4 48 mg/l, NaHCO_3 350 mg/l, NaCl 8000 mg/l, CaCl_2 140 mg/l, $\text{MgCl} \cdot 6\text{H}_2\text{O}$ 100 mg/l, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 148 mg/l, $\text{CH}_2\text{OH}(\text{CHO})_4\text{CHO}$ 1000 mg/l) for cyclic polarization. For wear corrosion tests, a 50 g dead-weight ruby ball was applied at 10 rpm. It was found that (i) pitting corrosion resistance can be improved by ion implantation modification, (ii) wear corrosion resistance was improved through ion implantation and heat treatment, and (iii) nanopores (3×10^{17} ions/ cm^{-2}) are introduced on the material surface at higher dose ion implantation, acting as the source of pitting corrosion and impairing pitting corrosion resistance [101].

The corrosion performance of NiTi SME alloy in human body simulating fluids (BSF) was evaluated in comparison with other implant materials (Ti–6Al–4V, Co–Cr, stainless steel) by Rondelli [110]. As for the passivity current (i.e., current density for passivation onset) in potentiostatic conditions, it was noted that the value is about three times higher for NiTi than for Ti–6Al–4V and stainless steel. Regarding the localized corrosion, while potentiodynamic scans indicated that for the NiTi alloy, good resistance to pitting attack which is similar to Ti–6Al–4V and the scratch tests by abruptly damaging the surface passive film (i.e., potentiostatic scratch test and modified ASTM F746) pointed out that the characteristic of

the passive film formed on NiTi alloy are not as good as those on Ti–6Al–4V but are comparable or inferior to those on austenitic stainless steels (like 304L or 316 type stainless steels) [110]. Therefore, it is suggested that self-healing (i.e., repassivation) capability of NiTi was inferior to that of Ti–6Al–4V.

Moreover, there are studies on corrosion behaviors of heavily alloyed Ti materials. Three Ti-based alloys (50.7Ni–49.4Ti, 51.4Ni–48.4Ti–0.19Cr, and 45.1Ni–49.6Ti–0.29Cr–4.97Cu) were electrochemically evaluated in 0.9% NaCl and 1% lactic acid solutions. It was concluded that small amounts of Cr and Cu changed the superelastic characteristics but did not change the corrosion resistance of the NiTi alloy [111]. Using the ASTM F746 “scratch” test, in 40°C 0.9% NaCl solution [112], 50Ni–50Ti, 44Ni–51Ti–5Cu, and 88Ti–6.5Mo–3.5Zr–2Sn [113] were examined through electrochemical tests. It was concluded that (i) both NiTi and NiTi–Cu wires exhibit low corrosion potential (50–150 mV vs. SCE), indicating an inferiority to that of TiMo alloy (which agreed with results reported in [110]) and (ii) TiMo proved to be immune to localized corrosion attacks up to 800 mV [113].

Different electrochemical studies were carried out for Zr, Ti–50 at.% Zr (or Ti–65.6 wt% Zr) and Zr–2.5 wt% Nb in solutions simulating physiologic media—Ringer’s solution and phosphate-buffered saline (PBS) solution. The results from rest-potential measurements showed that (i) the three materials are spontaneously passivated in both solutions and (ii) the Ti–50Zr alloy has the greatest tendency for spontaneous oxide formation, which could be a mixture of ZrO_2 and TiO_2 . Some corrosion parameters (such as the pitting and repassivation potentials) were obtained via cyclic voltammetry in both solutions, revealing that the Ti–50Zr has the best corrosion protection while Zr has the worst. On the other hand, it was reported that the preanodization (up to 8 V vs. SCE) of the alloys in a 0.15 mol/l Na_2SO_4 solution led to a significant improvement in their protection against pitting corrosion when exposed to the Ringer’s solution [114].

In the last decade, the AC EIS technique has been utilized more frequently in corrosion studies. The *in vitro* and *in vivo* electrochemical behaviors of CpTi were characterized using a specialized osseous implant in conjunction with EIS measurement techniques. Capacitance and polarization resistance measurements by EIS methods suggested that a biofilm formed on the surface of CpTi in *in vivo* and *in vitro* situations is passive and stable [115]. The corrosion behaviors of CpTi, Ti–6Al–4V, and NiTi were studied in a buffered saline solution using anodic polarization and EIS techniques [116]. Pitting potential as low as +250 mV (vs. SCE) was recorded for Ti–45Ni. The initiated pits continued to propagate at potentials as low as –150 mV (vs. SCE). It was possible to increase the pitting potential of Ti–45Ni to values greater than +800 mV using a H_2O_2 surface treatment procedure; however, due to unstable passivation, this surface modification process had no beneficial effect on the rate of pit repassivation. It was reported that the surface oxide layer consists of a porous outer layer and an inner barrier layer. The nature of this porous layer was found to depend on the nature of the electrolyte material and the presence of phosphate anions in the saline-buffered solution. Much higher porous layer resistances were recorded for CpTi and also for Ti–6Al–4V in the absence of the phosphate anions [116].

As mentioned above, the addition of protein in corrosion media would alter the corrosion behavior remarkably. The ability of Ti–6Al–4V, Ti–13Nb–13Cr, and Ti–6Al–7Nb to repassivate was investigated in PBS, bovine albumin solutions in PBS, and 10% fetal calf serum in PBS at different pH values and at different albumin concentrations by Khan et al. [117]. It was concluded that (i) an increase in pH had a greater effect on the corrosion behavior of Ti–6Al–4V and Ti–6Al–7Nb than Ti–13Nb–13Cr in PBS, (ii) the addition of protein to the PBS reduced the influence of pH on the corrosion behavior of all the alloys, and (iii) the proteins in the environment appear to interact with the repassivation process at the surface of these alloys and influence the resulting surface properties [117].

Furthermore, the effect of proteins on corrosion rates of 316L stainless steel, CpTi, and Ti–6Al–4V was studied in the static and fretting modes. It was reported that (i) proteins had an insignificant effect on the static corrosion rate of Ti–6Al–4V samples but caused a 31% increase in $1/R_p$ (a reverse of polarization resistance and hence a reverse of corrosion resistance) of the CpTi samples and (ii) for both CpTi and Ti–6Al–4V specimens, the presence of proteins had an insignificant effect on corrosion rates in the fretting mode [50].

Williams and others [73,74] prepared the protein solutions using crystallized bovine albumin and 95% clottable bovine fibrinogen. These were made up as 0.1% solutions in a buffer composed of 0.1 M sodium chloride and 0.01 M sodium phosphate at pH 7.4. Pure metallic elements (Al, Co, Cu, Cr, Mo, Ni, and Ti) were examined in the prepared solution. It was concluded that (i) serum albumin and a small amount of fibrinogen can have a significant influence on the corrosion behavior of metals, (ii) with some metals, such as Co and Cu, the corrosion rate increased significantly, (iii) with Cr and Ni the rates are moderately raised, but with Mo, the corrosion is inhibited, and (iv) there is little effect on Al and Ti [73,74], which are normally covered with the passive oxide films.

Biotribology (friction, wear, and lubricant actions in a biological environment) is becoming an important concern; in particular, the toxicity of wear debris (likely as toxicity of corrosion products) should be considered.

Metallic implants inserted into the body will eventually undergo some degradation by a variety of mechanisms including abrasion and corrosion. The biological effect of the material released into the tissue is a subject of much concern and investigation. It is apparent that many patients have sensitivity (and some of them develop a hypersensitivity) to the metals in the implants and that the presence of metal(s) in a sensitive animal or human will elicit inflammatory responses and sometimes the formation of foreign body giant cells. This may have an adverse effect on the performance of the implant with pain, swelling, and tissue necrosis at the site, and, in some cases, loosening of the implant. Metal sensitivity reaction is not to the small metal ions but to a complex of metal ions and host tissue. The nature of the bonding of the metal ion to tissue or cells, the distribution of the metal ions or metal complexes in the body, and the biological responses to these complexes are of concern. According to Khan et al. [118], the *in vitro* and *in vivo* studies were undertaken on the binding of metal ions as metal salts or as corrosion products, and it is evident that metals bind mostly to albumin. The ability of these

different metals to bind to red cells and white cells varies, with Cr^{6+} binding most strongly to cells. The chrome from corrosion products binds strongly to cells and thus appears to be a Cr^{6+} . The interaction of serum and cells with chromium on the surface of the implant may markedly effect its corrosion and the biological activity of the complexes formed. Some of the tissue and protein may be altered by changes in the tissue pH during inflammatory responses or infection [118].

Wear debris has been implicated in the pathogenesis of loosening and the osteolysis of total joint replacements by stimulating a foreign body and chronic inflammatory reaction capable of bone resorption. Effects of wear particles on bone have not been well documented. It was reported that 316 stainless steel exhibited wear toxicity by detecting Ni, Mn, and Cr ions dissolved out of stainless steel, while no Ti ion was detected to be dissolved from the wear debris [119]. A presence of the wear debris depends strongly on the wear resistance of materials. Khan et al. [120] performed the sliding wear tests in both noncorrosive and corrosive environments. A simple pin-on-disc type of wear apparatus was designed and built to simulate the co-joint action of corrosion and sliding wear. It was found that (i) the mixed phase α - β alloys (Ti-6Al-4V and Ti-6Al-7Nb) possessed the best combination of both corrosion and wear resistance and (ii) CpTi and the near- β (Ti-13Nb-13Zr) and β (Ti-15Mo) alloys displayed the best corrosion resistance properties [120].

Goodman et al. [121] performed a histomorphological and semi-quantitative morphometric analysis of the reaction of bone to different concentrations of phagocytosable particles of high-density polyethylene (averaged particle size: $4.7 \pm 2.1 \mu\text{m}$) and Ti-6Al-4V alloy implanted in a rabbit tibia. Suspensions of 10^6 – 10^9 particles per ml were mixed in saline, sterilized, and introduced into the proximal tibia of 30 mature female rabbits for 16 weeks. It was found that (i) phagocytosable particles of Ti-6Al-4V and high-density polyethylene, in concentrations of 10^6 – 10^9 particles per ml, induced a histocytic reaction without extensive fibrosis, necrosis, or granuloma formation and (ii) this reaction occurred without disturbing the normal repair processes of bone formation and resorption to the surgical insult [121].

There are, lastly, studies on corrosion–fatigue interactions. To clarify the influence of NaCl aqueous solution in corrosion fatigue crack initiation of mill-annealed Ti-6Al-4V, Ebara et al. [122] conducted rotating-bending fatigue tests of notched specimens with stress concentration factors in the range 1.5–3.5, in aerated and deaerated 3% NaCl solutions at 80°C. Ultrasonic fatigue tests up to 10^{10} cycles were also conducted in aerated 3% NaCl solution at room temperature. It was reported that the fatigue limit in air and corrosion fatigue strength at 10^8 cycles decreased with increases in the stress concentration factor. The reduction in fatigue strength of the notched specimen ($K_t = 3.5$) by the environment at 5×10^7 cycles was almost 20%. No differences between aerated and deaerated conditions were observed. It was therefore concluded that (i) corrosion fatigue crack initiation of the notched Ti-6Al-4V was predominantly influenced by the stress concentration factor and not by chlorine ions or dissolved oxygen content in the NaCl aqueous solution and (ii) fatigue crack initiation of Ti-6Al-4V was not significantly influenced by the NaCl solution at room temperature even in long fatigue life up to 10^{10} cycles [122].

Removable partial dentures (made of CpTi or Ti–6Al–4V) are affected by fatigue because of the cyclic mechanism of masticatory system and frequent insertion and removal. Ti materials have been used in manufacturing of denture frameworks; however, preventive agents with fluorides are considered to attack Ti materials, as discussed previously. Tests were done at 70% load of the 0.2% off-set yield strength in room temperature synthetic saliva and fluoride-added synthetic saliva. It was found that (i) Ti–6Al–4V achieved 21,269 cycles against 19,175 cycles for CpTi, (ii) there were no significant differences between either metal in corrosion–fatigue life for dry specimens, and (iii) when the solutions were present, the fatigue life was significantly reduced, probably because of the production of corrosion pits caused by superficial reactions [123], providing a localized stress-concentrated site and, therefore, a potential crack initiation site.

Ntasi et al. [124], studying the effect of electro discharge machining (EDM) on the corrosion resistance of dental alloys (Co–Cr alloy and grade II CpTi) in Ringer's solution, found that (i) conventionally machined surfaces were passive in a wide range of potential demonstrating higher polarization resistance and lower corrosion current density and (ii) the EDM procedure decreases the corrosion resistance, thus increasing the risk of possible adverse biological reactions.

Not only solid titanium materials but also titanium oxide was subject to corrosion evaluation. Yu et al. [125] studied the corrosion behavior of TiO₂ nanotube layers on titanium in Hank's solution, using EIS technique and potentiodynamic polarization method too. It was reported that (i) TiO₂ nanotube layers on titanium showed a better corrosion resistance in simulated biofluid than that of smooth CpTi, (ii) anatase nanotube layer showed higher open-circuit potential and smaller corrosion current density than the amorphous nanotube, and (iii) titanium with TiO₂ nanotube layers has an adequate electrochemical behavior for use as a dental implant material [125].

Popa et al. [126,127] had conducted a long-term monitoring at the interface between biomaterial surfaces (CpTi, Ti–5Al–4V, Ti–6Al–4Fe) and biological liquids for 20,000 exposure hours (ca. 2 years and 4 months). Biological media were Ringer's solutions with two different pH values [126] and Carter–Brugirard artificial saliva [127]. It was reported that (i) ion release increased with time, for the first 400–600 immersion hours, and then tended to a constant level with very low values, (ii) surface roughness increased with time and in the presence of the fluoride ions, denoting some increase in the anodic activity, and (iii) the existence of protective titanium dioxide TiO₂ and TiO and Ti₂O₃ oxides both for CpTi and Ti–5Al–4V alloy was detected.

3.5 Metal Ion Release and Dissolution

From the biological point of view, titanium is a strange element. It is widely distributed in the earth's crust and yet exists in only minimal amounts in animal and plant tissues. There is no evidence to suggest that it is an essential trace element,

but on the other hand, it is extremely well tolerated by tissues and is essentially nontoxic. There is no clear evidence of titanium metabolism. It may, therefore, be described as a physiologically indifferent metal. With this characteristic, coupled with the excellent corrosion resistance, it is known that titanium materials exhibit excellent biocompatibility [128]. Knowledge about the release of various elements from metallic biomaterials in the oral cavity with respect to levels, kinetics, and chemical state is essential in the evaluation of possible local or systemic effects pertinent to individuals having such biomaterials as dental prostheses, dental implants, and orthopedic devices and implants. Certain types of metallic biomaterials are suspected of being associated with allergies or may influence the number of T-lymphocytes, possibly affecting the immune system [129]. When metal ions are released, some stay in the local implant site, while others are transported in the blood. Blood-borne elements may remain in the blood as cell complexes, accumulate in organs, or be excreted by sweat or urine. Metal ions are known to be toxic, sensitizing, and oncogenic [130].

During the corrosion process, metallic ion(s) can be released from the substrate surface area, causing the dissolution into corrosive media or surrounding tissue (if the case is for implant). Hence, ion release is directly related to the stability of surface oxide (passive film) formed on the titanium substrate, and the capability for repassivation when such a stable passive film is disrupted. On the polarization process, there should be two occasions when ions can be released (in other words, instability of passivation): when active dissolution prior to the onset of passivation occurs at relatively low potential and when there is transpassivity (or breakdown of stable passive film) at relatively high potential. For example, the transpassivation occurs at or higher than 1.5 V (vs. SCE), depending on the electrolyte and type of titanium materials used. Such transpassivation is normally accompanied by the formation of pits.

Though the metals used in implants are quite corrosion resistant, there is still some interchange of metal ions into the tissues or tissue fluids [131]. The amount of metal ions released is related to the corrosion resistance of the metal, the environmental conditions (i.e., pH, chloride ion concentration, temperature), mechanical factors (i.e., preexisting cracks, surface abrasion, film adhesion), electrochemical effects (i.e., applied potential, galvanic effects, pitting or crevices), and the dense cell concentrations around implants. When an implant protrudes through the tissue, the electrochemical effects may be even more severe. Implants that undergo fretting wear provide the possibility of releasing more ions into solutions than those that do not due to the stress-assisted dissolution. The response of the tissues and the entire body to metal ions has been studied and continues to be an active area of biomaterials research [131]. Certain metal ions have been shown to be more harmful than others. The response of local tissues to metal ions is usually short term, while accumulation of metal ions in more remote tissues such as the kidney, liver, or blood may require a longer time. Systemic effects characterized by sensitization may also occur due to the body's interaction with the metal ions. Titanium, which has a very strong, adherent, semi-amorphous surface oxide film, has been found by neutron activation analysis in some of the tissues surrounding titanium implants

[132]. The clinical, radiologic, and laboratory records of the patients were carefully reviewed and it was found that titanium does not seem to have a particularly harmful effect on local tissues. The systemic effects and sensitization response attributed to titanium seem to be minimal as well [132].

The biological significance of the metal ion release is believed to be strongly related to the cytocompatibility and hemocompatibility. It is also generally believed that corrosion resistance is responsible for the biocompatibility. Tissue levels of chromium and titanium are often very high indicating that the elements may form stable complexes that remain in local tissues [130]. Woodman et al. [133] reported a significant increase in serum aluminum but no increase in titanium and vanadium from porous-coated Ti–6Al–4V implants in baboons. It was also reported that (i) high levels of titanium were found in lung and liver tissue, as well as regional lymph nodes, (ii) a substantial and progressive increase in aluminum content was found in lung nodes of baboons with porous Ti–6Al–4V implants, and (iii) titanium levels in the urine of baboons increased with porous titanium implants, but no significant increases were found in the levels of vanadium or aluminum [133].

An important factor related to the biocompatibility of metallic implants is the metal ion release rate from their surfaces. *In vitro* laboratory tests are often used to estimate the corrosion rates of implant materials. For these to be useful in predicting *in vivo* ion release, however, they should simulate *in vivo* conditions as closely as possible. Bundy et al. [134] pointed out that a variable often not accounted for in such testing is the influence of applied stresses. The effect of static stresses on the corrosion behavior of 316L stainless steel, Ti–6Al–4V, and Co–Cr–Mo alloy was investigated. The stress ratio ($\sigma_{\max}/\sigma_y$) was selected in a range 1.2–1.4; hence, all sample surfaces were subjected to a plastic deformation. Although loading over the yield strength causes stress-enhanced ion release, it was mentioned that the stress-induced ion release may also be caused by elastic loading. The basic mechanisms for this phenomenon appear to be passive film disruption followed by slow repassivation kinetics. Occurrence of pitting corrosion indicates that the surface oxide film was broken and does not protect the underneath substrate. If effects similar to those observed apply to *in vivo* conditions, it was suspected that tests on unstressed alloys *in vitro* could grossly underestimate ion release rates of stressed implant devices *in vivo* [134]. It was also mentioned that ions are released but not necessarily in proportion to the alloy composition. Ni and Co bind to serum albumin, whereas Cr is released with a valence of 6^+ and binds to red blood cells. Tissue levels of Cr and Ti are often very high indicating that these elements may form stable complex that remain in local tissues. The results of chemical analysis of urine from animals exposed to metal ions from injection of salts *in vivo* corrosion demonstrates a rapid excretion of Ni and Co; excretion of Cr is slow and represents a small percentage of the total to which the animal is exposed [134]. The repassivation capability *in vitro* should not be the same as that found in the *in vivo* situation, since there are many evidence indicating that the oxide film formed on the placed Ti implant increases its thickness 7–20 times, due to more oxygen availability *in vivo*, as seen in Chapter 4.

The metallic ion release from dental alloys has been transformed into one of the major problems in the health of dental patients who have metallic materials fitted in their mouths [135]. It is well known that metals are toxic in sufficient concentration and that they can cause inflammations [136], allergies, genetic mutations, or cancer [137]. The metallic elements that are released from oral implants have been detected in the tongue [136], the saliva [138], and in the gums adjacent to these alloys [139, 140]. However, it is not a case of a local problem but a rather general one due to their diffusion throughout the whole organism. The ions are conducted and can be excreted in part or entirely, or they may be accumulated selectively at the level of certain tissues [128,133]. The harmful effects of certain metals and metallic composite materials were made clear in the epidemiological studies carried out by the nickel, chromium, cobalt, and copper industries and confirm that the action of metals in the form of ions, particles, and soluble or insoluble salts act at the cellular membrane level [141]. Metals from orthopedic implants are released into surrounding tissue by various mechanisms, including corrosion, wear, and mechanically accelerated electrochemical processes such as stress implant failure, osteolysis, cutaneous allergic reactions, and remote site accumulation. Okazaki and Gotoh [141] investigated the metal ion release from 316L stainless steel, Co–Cr–Mo, CpTi (grade II), Ti–6Al–4V, Ti–6Al–7Nb, Ti–15Zr–4Nb–4Ta at 37°C in PBS solution, 0.9% NaCl aqueous solution, 1.2% L-cysteine solution, 1% lactic acid solution, and 0.01% HCl solution. It was concluded that (i) the quantity of Co released from the Co–Cr–Mo casting alloys was relatively small in all the solutions, (ii) the quantities of Ti released into PBS, calf serum, 0.9% NaCl, and artificial saliva were much lower than those released into 1.2% L-cysteine, 1% lactic acid, and 0.01% HCl, (iii) the quantity of Al released from the Ti alloys gradually decreased with increasing pH, and a small amount of V was released into calf serum, PBS, artificial saliva, 1% lactic acid, and 0.01% HCl, and (iv) Ti–15Zr–4Nb–4Ta alloy, with its low metal release, is considered advantageous for long-term implants [141].

Ti-based implant materials show very high resistance to pitting corrosion in physiological solutions because of their state of passivity [142,143]. The effect of temperature on the nucleation of corrosion pits on CpTi in Ringer's solution was investigated. Breakdown of the passivity (or transpassivation) of CpTi by nucleation of corrosion pits occurs in Ringer's solution at quite modest electrode potentials. It was reported that (i) the frequency of breakdown is very low at ambient temperature but increases significantly with an increase in temperature (e.g., 20°→37°→50°C) and (ii) the very slow overall release rate estimated from the data is consistent with previously measured release rates [142]. The vanadium-free Ti–15Zr–4Nb–4Ta alloy, containing 0.2Pd and Ti–6Al–4V ELI, were implanted in rat tibiae for 6–48 weeks. It was found that (i) the number of corrosion pits observed at the Ti–6Al–4V ELI alloy surface tended to be slightly more than that of the Ti–15Zr–4Nb–4Ta alloy implant and (ii) the concentrations of metal elements in the bone tissue containing the new bone tended to increase slightly more than in bones without the implants [144].

The formation of pits is related to the equilibrium potentials of (passive) film formation given as a function of the activities of the components of the film substance. The solubility of the product, with respect to the ions in the electrolyte, depends on the electrode potential, since oxidation states of the metal in the film and in the electrolyte are often different. Heusler [145] discussed the kinetics of uniform film formation and dissolution with respect to (1) equilibrium of all components across both interfaces, (2) partial equilibrium of one component at the outer film/electrolyte interface, and (3) irreversible ion transfer reactions at the outer interface. Examples are oxide films on iron (i.e., Fe_2O_3 and/or Fe_3O_4), titanium (TiO_2), and aluminum (Al_2O_3). It was mentioned that the processes during the incubation time (which should include chlorine ion adhesion and absorption) of pitting corrosion corresponded to nonuniform dissolution and formation of the passivating film [145].

Hence, it is important to form stable passive films to control the metal ion release. Chang and Lee [146] prepared as-received Ti–6Al–4V and modified Ti–6Al–4V with 300 μm thickness containing Cu and Ni by vacuum brazing at 970°C for 2 h and tested them in Hank's solution (NaCl 8 g, CaCl_2 0.14 g, KCl 0.4 g, NaHCO_3 0.35 g, glucose 1 g, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 0.1 g, $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ 0.06 g, KH_2PO_4 0.06 g, and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 0.06 g) with 8 mM ethylene diamine tetraacetic acid (EDTA) at 37°C for immersion times of 1, 4, and 16 days. It was noted that the variation of chemical compositions of the alloy and nanosurface characteristics (chemistries of nanosurface oxide, amphoteric OH group adsorbed on oxides, and oxide thickness) was affected by surface modification and three passivation methods (34% HNO_3 passivation, 400°C heating in air, and aged in 100°C water). It was concluded that (i) passivation influences the surface oxide thickness and the early stage of ion dissolution rate of the alloy, (ii) the rate-limiting step can be best explained by metal ion transport through the oxide film, rather than hydrolysis of the film, and (iii) variations of the chemistries of Ti alloy alter the electromotive force (EMF) potential of the metal, thereby affecting the corrosion and ion dissolution rate [146].

There is other evidence strongly supporting the importance of surface oxide to govern the ion release kinetics. During implantation, Ti releases corrosion products (which can be TiO , TiOH , or TiO_2) into the surrounding tissues and fluids even though it is covered by a thermodynamically stable oxide film. An increase in oxide thickness as well as the incorporation of elements from the extracellular fluids (P, Ca, and S) into the oxide has been observed as a function of implantation time. Moreover, changes in oxide stoichiometry, compositions, and thickness have been associated with the release of Ti corrosion products. Properties of the oxide, such as stoichiometry, defect density, crystal structure and orientation [147], surface defects, and impurities were suggested as factors determining biological performance [148].

From the above discussion, it can be clearly stated that passivation stability can control the ion release kinetics under some factors such as chlorine ions, causing a premature passivation breakdown, as well as the formation of pits. Stable passivation can also be interfered by mechanical or physical actions [149,150]. Okazaki [149]

studied the effects of frictional forces on anodic polarization properties of several metallic biomaterials in eagle's medium and 1% lactic acid solutions. The results on Ti–6Al–4V demonstrated that, under static condition (in other words, no frictional force applied), I_{PASS} (passivation onset current density) was 4×10^{-6} A/cm², E_{PASS} (passivation potential) was about -400 mV (vs. SCE), and the established passivation was stable up to E_{BK} (breakdown potential of passivation) of 2000 mV (vs. SCE). However, when a kinetic frictional force of 20 N was applied, E_{PASS} (-700 mV) was about the same as the static E_{PASS} , and I_{PASS} showed a wide fluctuation between 2 and 7×10^{-5} A/cm² up to E_{BK} of approximately 2100 mV (vs. SCE). Oshida et al. [150] had investigated the effects of ultrasonic vibration on passivation stability. CpTi (grade II) plates were polarized in an artificial saliva solution with and without ultrasonically vibrating the electrolyte. It was found that, under no vibration conditions, stable passivation was obtained from E_{PASS} of 150 mV (vs. SCE) up to E_{BK} of 1100 mV (vs. SCE). On the other hand, under vibration conditions, CpTi did not exhibit a stable passivity all the way up to 1500 mV (vs. SCE). Hence, the mechanical vibration hinders the stable establishment of passivation of the CpTi surface in 25°C artificial saliva solutions [150].

For different Ti material groups, there are several reports on ion release data. Levels of corrosion products released from dental alloys in natural or synthetic saliva (i.e., from amalgams, cobalt, gold, nickel, iron, or titanium-based alloys) have been surveyed [129]. The corrosion behavior in the oral cavity is complex and involves several parameters, including, for example, composition and treatment of the alloy, pH, and oxygen variations in the oral cavity, presence of proteins, masticatory function, etc. Corrosion products and particles released from dental alloys in the oral cavity are eliminated from or absorbed by the human body. Thus, specific metals that may be accumulated within human tissues are subsequent to resorption in the gastrointestinal tract following the swallowing of saliva, after membrane diffusion in the Okla mucosa, or after migration to pulp through dentinal tubuli [130]. The amounts of implanted titanium that could be released into an electrolyte-like artificial saliva seem, however, to be far from the intake of the element from food and drink. It is known that aluminum and titanium released from titanium alloy implants in baboons can accumulate in the lung tissue [151–153]. Titanium levels up to about 1000 ppm (dry weight) have been measured in osseous tissue surrounding various titanium implant materials after 6 months exposure in the trabecular bone of German shepherd dogs [154].

In studies done by Strietzel et al. [155], cast CpTi (grade I) samples were subjected to immersion–corrosion tests for 4 weeks in NaCl (sodium chloride), NaF (sodium fluoride), NaSCN (sodium thiocyanate), lactic acid, acetic acid, oxalic acid, and tartaric acid. Atomic absorption was used to analyze the solutions weekly. It was noticed that (i) Ti reveals ion releases [$(0.01\text{--}0.1) \mu\text{g}/(\text{cm}^2 \text{d})$] in the magnitude of gold alloys, (ii) there is little influence of grinding and casting systems in comparison with organic acids or pH value, (iii) the ion release greatly increases (up to $500 \mu\text{g}/(\text{cm}^2 \text{d})$) in the presence of fluoride; and low pH values accelerate this effect even more, (iv) nevertheless, it is recommended that it is best to avoid

the presence of fluoride or to reduce contact time, and (v) in prophylactic fluoridation of teeth, a varnish should be used [155].

In vitro metal leaching examinations were performed for Ti from CpTi, Ti, Al, and V from Ti–6Al–4V alloy, and Ti and Pd from CpTi (grade VII), for 7 days. It was found that in general (i) the low leaching of Ti, Al, and V metal ions and the absence of Pd from the different surfaces indicated excellent protection against corrosion by the surface oxide layer of Ti₂O₃ and (ii) the leaching of Ti, Al, and V from metal surfaces over 7 days in an isotonic medium indicated the possibility that leaching of metal ions may have detrimental effects on general health, suggesting the need for long-term studies on accumulation and toxicity of metal ions from various metal surfaces [156].

Although osteolysis adjacent to metal hip and knee prostheses is believed to result from release of wear debris into the periprosthetic region, it is suspected that metal ions released from the implant surface may also play some contributing role [134,148,157–159]. This suspicion arose in part from various retrieval studies of human total hip arthroplasties, which have shown that metal levels in the tissue surrounding metal implants are fairly high. Dorr et al. [160] have measured metal levels in the fibrous membrane encapsulating implants at up to 21 ppm Ti, 10.5 ppm Al, and 1 ppm V around Ti–6Al–4V and up to 2 ppm Co, 12.5 ppm Cr, and 1.5 ppm Mo around Co–Cr–Mo. Henning et al. [161] have found metal levels in the tissue surrounding loose Co–Cr–Mo femoral shafts to average 3.5 ppm Cr and 0.9 ppm Co. It was also reported that (i) metal ions released from the implant structure are suspected of playing some contributing role in loosening of hip and knee prostheses, and (ii) sublethal doses of the ionic constituents of Ti–6Al–4V alloy suppressed the osteoblastic phenotype and deposition of a mineralized matrix [162]. Thompson and Puleo [157] harvested bone marrow stromal cells from juvenile rats and exposed them to time-staggered doses of a solution of ions representing Ti–6Al–4V alloy. Cells were cultured for 4 weeks and assayed for total protein, alkaline phosphatase, intra- or extracellular osteocalcin, and calcium. It was found that (i) the Ti–6Al–4V solutions were found to produce little difference from control solutions for total protein or alkaline phosphatase levels but strongly inhibited osteocalcin synthesis, and (ii) calcium levels were reduced when ions were added before a critical point of osteoblastic differentiation (between 2 and 3 weeks after seeding). Based on these findings, it was concluded that ions associated with Ti–6Al–4V alloy inhibited the normal differentiation of bone marrow stromal cells to mature osteoblasts *in vitro*, suggesting that ions released from implants *in vivo* may contribute to implant failure by impairing normal bone deposition [157].

As for NiTi materials, it was reported that nickel ions were dissolved out [163,164]. Kimura and Sohmura [165] coated NiTi implants with oxide film to suppress dissolution of Ni and estimated the corrosion resistance in 1% NaCl solution by means of anodic polarization measurement. It was found that by coating (i) dissolution at low potential was suppressed and the dissolute current density decreased, (ii) a further decrease in current density, which results from stabilization of the passive state on the surface, was observed by the repeated polarization, and

(iii) the oxide film showed close adhesion with the matrix and did not form cracks or peel off by plastic deformation associated with the SME [165].

Huang et al. [166] evaluated four commercially available orthodontic superelastic NiTi wires in modified Fusayama artificial saliva—NaCl (400 mg/l), KCl (400 mg/l), $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (795 mg/l), $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (690 mg/l), KSCN (300 mg/l), $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (5 mg/l), and urea (1000 mg/l). The value of pH was adjusted to be 2.5, 3.75, 5.0, and 6.25 by either lactic acid or sodium hydroxide. Tests were conducted at 37°C for a duration ranging from 1 to 28 days. It was concluded that (i) the released amount of metal ions increased with immersion period, (ii) the amount of metal ions released in pH > 3.75 solution was much less than that in pH 2.5 solution, (iii) preexisting surface defects in NiTi wire might be the preferred sites for corrosion, while NiTi wire, with a rougher surface, did not exhibit a higher ion release [166], and (iv) the average amount of Ni ions released per day from the tested NiTi wires was well below the critical concentration necessary to introduce allergy (600–2500 μg) [167] and under daily dietary intake level (300–500 μg) [168].

As demonstrated in the reviews above, the stability of oxide film formed on the surface of Ti appears to be crucial in governing the ion release equilibrium, as well as kinetics. One can find several proposed methods and technologies to enhance the oxide stability, thereby improving the ion release resistance. Ti–6Al–4V, CpTi, and TiN-coated Ti–6Al–4V by electron beam PVD at 300–350°C were tested in 0.17 M NaCl plus 0.0027 M EDTA (ethyl-diamine tetraacetic acid, disodium salts) at 37°C. It was demonstrated that a substantial reduction in the release of metal ions may be achieved by aging the surface oxide in boiling distilled water or by thermal oxidation (400°C $\times$ 45 min in air) [147].

Healy and Ducheyne [148] prepared a titanium thin film (1 μm thick) by the deposition method onto silicon substrates by radio frequency sputter coating. Films were immersed into 23 ml of 8.0 mM ethyl-diamine tetraacetic acid in simulated interstitial electrolyte solution and placed in an incubator maintained at 37°C, 10% O_2 , 5% CO_2 and $97 \pm 3\%$ humidity. It was concluded that (i) the dissolution of titanium in the presently simulated physiological environment occurred in two phases and the transition between phases appeared after 200–400 h of immersion, (ii) coincident with this transition was the onset of nonelemental P incorporation into the oxide, (iii) the dissolution rate decreased as the oxide thickness increased for immersion times less than 50 h, and (iv) the dissolution reaction depended on chemical reactions, including (1) the hydrolysis of the oxide and the exchange reactions between the Ti–OH surface sites and (2) the adsorbed P-containing species [148].

Ti–6Al–4V offers an excellent combination of mechanical properties for load-bearing applications such as hip prostheses, but there is concern about the slow accumulation of potentially harmful metal ions (such as aluminum and vanadium) in the soft tissue surrounding the prosthesis [169]. Furthermore, there is evidence that tissue reactions adjacent to Ti–6Al–4V alloy are less natural than those in the vicinity of CpTi [170]. Metal ion release is considered to occur via chemical dissolution of the surface oxide film, and it was shown that the dissolution rate is influenced by passivation treatments and surface coating such as TiN [147,171]. These

effects may be associated with structural changes of the surface oxide. The aging of the oxide on the surface of CpTi, Ti–6Al–4V, and TiN-coated Ti–6Al–4V was investigated. Johansson et al. [170] studied the influence of the surface oxide on the dissolution of the substrate material in saline solution. It was demonstrated that (i) a substantial reduction in the release of metal ions may be achieved by aging the surface oxide which was treated in boiling distilled water or by thermal oxidation, and (ii) a reduction in the dissolution of metal ions from titanium-based implant materials in saline solution (0.17 M NaCl plus 0.0027 ml EDTA at 37°C) may be achieved by aging the surface oxide in boiling distilled water or by thermal oxidation. It was further speculated that the change in the dissolution behavior is associated with the transformation of the surface oxide of TiO₂ from the anatase form (tetragonal, $a = 0.378 \text{ \AA}$, $c = 0.951 \text{ \AA}$) to the more compact rutile structure (tetragonal, $a = 0.459 \text{ \AA}$, $c = 0.296 \text{ \AA}$) [171], since the c -axis ratio between anatase TiO₂ and rutile TiO₂ is 3.21, while a -axis ratio is only 1.21, so that the rutile structure is a more closed packed crystalline structure.

There is another study by Spriano et al. [172] on chemical and thermal surface modifications in order to control the metal ion release. The surfaces of Ti–6Al–7Nb were firstly sand blasted with corundum, followed by chemical treatments for passivation in 35 w% nitric acid for 30 min and in 5 M NaOH at 60°C for 24 h. Thermal treatments were also applied as an in-air oxidation at 600°C for 1 h in 5×10^{-1} bar. Studies on morphology, crystallographic structure, porosity and wettability, interaction with SBF, cytotoxicity, protein adsorption tests, *in vitro* fibroblast, and osteoblast-like cell culture were performed. It was concluded that (i) the surfaces treated by the blasted-passivated-in-air and *in vacuo* oxidation can be described as constituted by a microtextured oxide presenting high wettability and low metal ion release as well as moderate bone-like apatite induction ability, (ii) at the same time, a good chemical interaction of the surface with the culture medium, with a higher total protein binding than on the untreated one, was observed, suggesting that the multistep thermo-chemical treatment can be used as an alternative to traditional coatings in order to prepare low metal release prostheses with enhanced osteointegrability [172].

Titanium levels in the organs (heart, liver, spleen, kidneys, and lung) and blood of Wistar rats was monitored by double-focusing inductively coupled plasma mass spectrometry (ICP-MS) method [173]. Titanium has long been regarded as an inert and biocompatible metal, ideal for biomedical applications such as dental implants or joint replacements. However, concerns about the biocompatibility of Ti have lately arisen. Unfortunately, information on reliable Ti baseline physiological levels on blood and organ tissues is still pending and the real effects of physiological corrosion as opposed to wear processes of Ti and/or Ti alloys implants is controversial. Based on such important evidences, the double-focusing ICP-MS was employed to establish Ti basal levels in the blood and organs of rats, and data were compared with the levels found in rats implanted with a Ti wire embedded in the femur for 18 months. It was reported that Ti content in all the selected organ tissues and blood was higher than Ti basal levels, clearly indicating both corrosion of the Ti implant and systemic Ti accumulation in target tissues.

3.6 Galvanic Corrosion

There are two types of galvanic cell: the first type is the microcells (or local cells) and the second type is the macrocells. As for microcells, within a single piece of metal or alloy there exist different regions of varying composition and hence different electrode potentials. This is true for different phases in heterogeneous alloys [174]. The positive way of applying this phenomenon is by etching the polished surface of metal to reveal the microstructures for metallographic observations as severely deformed portion within one piece of a material can serve as an anodic site [175]. For example, a portion of a fully annealed nail was bent, and the whole nail immersed into a NaCl aqueous solution. After several hours, it was easily noticed that the localized plastic-deformed portion gets rusted. For macrocells, which occur at the contact point of two dissimilar metals or alloys with different electrode potentials, the so-called galvanic corrosion is probably the best known of all the corrosion types [174]. Titanium is the metal choice for implant material due to excellent tissue compatibility; however, superstructures of such Ti implants are usually made of different alloys. This polymetallism leads to detectable (in macro-level) galvanic corrosion.

The intensity of the galvanism phenomenon is due to a number of factors, such as the electrode potential, extent of the polarization, the surface area ratio between anodic site and cathodic site, the distance between the electrodes, the surface state of the electrodes, conductivity of the electrolyte, and passage of a galvanic current on the electrolytic diffusion, stirring, aeration or deaeration, temperature, pH and compositions of the electrolytic milieu, coupling manner, and an accompanying crevice corrosion. When two solid bodies are in contact, it is fair to speculate that there could be marginal gaps between them because they are not subject to any bonding method like diffusion bonding or fusion welding. Therefore, when the galvanic corrosion behavior is studied in a dissimilar material couple, the crevice corrosion is another important localized corrosion measurement accompanied by galvanic corrosion [175–181].

Among these numerous influencing factors, the surface area ratio between anodic surface and cathodic surface appears to be the most important factor to be considered. If the ratio of surface A_C/A_A (cathode area/anode area) is large, the increased corrosion caused by coupling can be considerable. Conductivity of the electrolyte and geometry of the system enter the problem because only that part of the cathode area for which resistance between anode and cathode is not a controlling factor is effective [181].

Al-Ali et al. [178] prepared CpTi (grade II) samples coupled with type IV Au alloy, Au–Ag–Pt alloy, and Ag–Au–Pd alloy, and effects of two coupling mode (laser welding and mechanical adhering method—in other words, without and with crevice situation between materials) and investigated their corrosion behaviors when electrochemically polarized in 37°C Ringer's solution. It was found that (i) significant differences in corrosion behavior were observed between the two different coupling methods, and crevice associated with adhesive joining made the

galvanic couples more corrosive, (ii) by the laser welding method, the values of coupled I_{CORR} (corrosion current density) for all three couples were somewhat in the middle of I_{CORR} values of uncoupled materials, while by the mechanical adhering method, the coupled I_{CORR} was higher than those for uncoupled CpTi as well as uncoupled precious alloys, (iii) a simplified mixed theory [179] was not applicable to estimate the mixed potential and current, (iv) the type IV gold side of the Ti/Au couple for both methods was discolored to some extent, and (v) overall, the Ti/Ag–Au–Pd couple exhibited the best corrosion resistance for both joining methods [178]. As for the effects of surface area ratio between anodic and cathodic metals [178,182], it was found that (i) I_{CORR} showed a bowl-shaped curve, (ii) I_{CORR} increased toward both ends (in other words, the uncoupled materials' sides), and (iii) I_{CORR} exhibited the lowest value when exposed surface areas of anodic and cathodic metals became equal.

There have been several reported failure cases of restorative devices due to a lack of understanding of galvanic or coupled corrosion properties of restorative materials [183,184]. As the success of implants leads to their increasing use in restorative dentistry, attention should be devoted to the galvanic combination of restorative materials with titanium [185]. At present, most of the literature shows that galvanic corrosion could occur when titanium is coupled to less noble alloys rather than more noble alloys and that the corrosion current density of the titanium was lowered by the lower current density of noble metal. The *in vitro* investigations of these materials have demonstrated susceptibility to galvanic corrosion phenomena. Thus, the integrity of restorative dentistry devices and intraoral prostheses may be comprised because of galvanic corrosion [186]. The depolarization effect when the materials were coupled was overcome by bubbling nitrogen through the artificial saliva solution. The nitrogen purge also reduced fluctuation in the oxygen concentration of the electrolyte [187,188]. It was hypothesized that the deaeration could also create a lack of oxygen for repassivation if a material's passive layer breaks down due to a galvanic coupling. This results in a reduced probability of the anodic component repassivating if its surface layer is disrupted. Crevices in such devices and wound sites have been documented to have, at the worst case, a pH of 3.0 or less [188–192]. When the two materials were coupled, the corrosion potential of both these materials converged to a common coupled corrosion potential [179]. This common potential was between the corrosion potentials of the materials involved in the couple. This is true for the case when at least one component in the couple is polarized [193]. The corrosion potential of the more noble material drops to the lower common corrosion potential value. This drop in potential of the noble component can serve as a driving force for the corrosion potential of the more active component to the higher coupled corrosion potential. Ti-based implant materials show very high resistance to pitting corrosion in physiological solutions because of their state of passivity [142,143].

The electrochemical behavior of seven alloy superstructures (including high and low Au-based alloys, Ag-based alloys, Co–Cr alloys) with CpTi and Ti–6Al–4V implants was tested in Fusayama–Meyer deaerated saliva and Carter–Brugirard nondeaerated saliva. It was found that very low corrosion rates were obtained,

ranging from 10^{-6} to 10^{-8} A/cm². Other possible types of corrosion are also considered a galvanic corrosion—for example, pitting corrosion and crevice corrosion. These types of corrosion are specific to each alloy and are to be taken into account in clinical choices. Moreover, the biological characteristics of each individual represent a variable which cannot be reproduced easily *in vitro* (composition and acidity of saliva, dental hygiene, eating habits, administration of medicine). For this reason, it was remarked that the most favorable superstructure/implant couple is the one which is capable of resisting the most extreme conditions that could possibly be encountered in the mouth [194].

Metal ions released in 1% lactic acid solution from combinations of titanium fixtures with superstructures made of dental precious metal alloys was investigated [195]. It was found that (i) in CpTi/Ti–6Al–4V combinations, differences in the microstructure of metal also markedly influenced the dissolution; the level or release increased when microstructure of titanium was different, (ii) the Ti and V release levels were higher in combination with Ti alloy and CpTi than with Ti alloy and dental alloys, and (iii), regarding the superstructure-fixture fixing method, the level of Ti release was significantly lower in cement than indirect fixation.

3.7 Microbiology-Induced Corrosion

Microbiology-induced corrosion (MIC) is defined as the deterioration and degradation of metallic structures and devices by corrosion processes that occur directly or indirectly as a result of the activity of living microorganisms, which either produce aggressive metabolites or are able to participate directly in the electrochemical reactions occurring on the metal surface. Corrosion has long been thought to occur by one of three means: oxidation, dissolution, or electrochemical interaction. To this list, the newly discovered microbiological corrosion must be added [196,197]. Oxidation is somewhat beneficial in the case of stainless steel (mainly the Cr element) and titanium because they create a nonporous layer of passive oxide film that protects the substrate surface from further oxidation; Cr₂O₃ or (Fe,Ni)O · (Fe,Cr)₂O₃ for stainless steel and TiO₂ for titanium materials. However, dissolution and electrochemical reactions are responsible for most of the detrimental corrosion. MIC has received increased attention from corrosion scientists and engineers in recent years. MIC is due to the presence of microorganisms on a metal surface which leads to changes in the rates and sometimes also the types of the electrochemical reactions that are involved in the corrosion processes. It is, therefore, not surprising that many attempts have been made to use electrochemical techniques (corrosion potential, the redox potential, the polarization resistance, the electrochemical impedance, electrochemical noise, and polarization curves including pitting) to study the details of MIC and determine its mechanism. Applications range from studies of the corrosion of steel pipes in the presence of sulfate-reducing bacteria to investigating the formation of biofilms and calcareous deposits on stainless steel in seawater, to the destruction of concrete pipes in sewers by microorganisms

producing very low pH solutions, to dental prostheses exposed intraorally to various types of bacteria [198,199].

The study of MIC is a typical interdisciplinary subject that requires at least some understanding of the fields of chemistry, electrochemistry, metallurgy, microbiology, and biochemistry. In many cases, microbial corrosion is closely associated with biofouling phenomena, which are caused by the activity of organisms that produce deposits of gelatinous slime or biogenically induced corrosion debris in aqueous systems. Familiar examples of this problem are the growth of algae in cooling towers and of barnacles, mussels, and seaweed on marine structures. These growths either produce aggressive metabolites or create microhabitats suitable for the proliferation of other bacterial species, for example, anaerobic conditions favoring the well-known sulfate-reducing bacteria. In addition, the presence of growths or deposits on a metal surface encourage the formation of differential aeration or concentration cells between the deposit and the surrounding environment, which might stimulate existing corrosion processes [196]. It is probable, however, that microbiological corrosion rarely occurs as an isolated phenomenon but rather is coupled with some type of electrochemical corrosion. For example, corrosion induced by sulfate-reducing bacteria usually is complicated by the chemical action of sulfides. Corrosion by an aerobic organism, by definition, always occurs in the presence of oxygen. To further confound the problem, microbiocidal chemicals also may have some conventional properties as corrosion inhibitors (e.g., film forming). The materials on which a biofilm is developed have higher, or more noble, E_{CORR} (potential at corrosion current) values than those obtained in the absence of biofilms [200].

Microbes seem to accelerate the corrosion process. They locate susceptible areas, fix anodic sites, and produce or accumulate chemical species that promote corrosion. The microscopic heterogeneity of many materials—whether created intentionally or as an artifact—is quite clear on the scale of microbes and is an important and overlooked factor in microbiologically influenced corrosion. Weld regions are particularly attractive to microbes in many of the systems [201], since the weldline normally exhibits slight differences in chemical compositions as well as microstructures, resulting in a possibility for galvanic corrosion occurrence. Microbes are extremely tenacious. They can exist over a wide range of temperatures and chemical conditions, are prolific, and can exist in large colonies. They form synergistic communities with other microbes or higher life forms and accomplish remarkably complex chemical reactions in consort. Microbes can metabolize metals directly, and they require many of the chemical species produced by the physical chemistry of corrosion processes for their metabolisms. Microbes can also act to depolarize anodic or cathodic reactions, and, in addition to catalyzing existing corrosion mechanisms, many microbes produce organic or mineral acids as metabolic products [201]. Accordingly, it is difficult to specify just what the important variables are when corrosion is influenced by microorganisms. In addition to the variables most important for the type of corrosion under consideration, variables such as dissolved oxygen, pH, temperature, and nutrients that affect the life cycle of the bacteria become important for both corrosion testing and corrosion mechanism. The critical situation involved in MIC is limited to the interfacial thin

layer (usually with thickness in the 10–500 μm range) between the biofilm and metallic surface, since the chemistry of the electrolyte solution at the metal surface is everchanging. Therefore, the bulk electrolyte properties may have little relevance to the corrosion as influenced by organisms within the film. The organism right at the metal surface influences corrosion activity, and those organisms multiply so rapidly on the surface that a low density of organisms in the bulk quickly becomes irrelevant [202].

Bacteria must adhere, spread, and proliferate on metallic surfaces in order to cause corrosive reactions. The process of bacterial adhesion is mediated by both an initial physiochemical interaction phase (i.e., electrostatic forces and hydrophobicity) and specific mechanisms (i.e., adhesion–receptor interactions, which allow bacteria to bind selectively to the surface) followed by a subsequent molecular and cellular interaction phase, which is normally followed by a plaque formation in dentistry [203]. The molecular and cellular interaction are complicated processes affected by many factors, including the characteristics of the bacteria themselves, the target material surface, and environmental factors such as the presence of serum proteins or bacterial substances. Microbial adhesion to surfaces is a common phenomenon. Many bacteria demonstrate a preference for the surface regions of solids, teeth, plant fibers, roots, and so on where nutrients may be concentrated by the adsorption of dissolved organic material. Since microorganism acts as colloidal particles, their interaction with solid surfaces can be anticipated, based on colloidal theory. However, microorganisms are more complex than typical colloids as they are capable of independent locomotion, growth in different shapes, and production of extracellular polymeric materials that aid in anchoring the microbe to the surface [203]. Adhesion is a situation where bacteria adhere firmly to a surface by complete physiochemical interactions between them, including an initial phase of reversible physical contact and a time-dependent phase of irreversible chemical and cellular adherence [204]. Bacteria and other microorganisms have a natural tendency to adhere to surfaces as a survival mechanism. This can occur in many environments including the living host, industrial systems, and natural waters. The general outcome of bacterial colonization of surfaces is the formation of an adherent layer (biofilm) composed of bacteria embedded in an organic matrix [205]. The starvation and growth phase influence bacterial cell surface hydrophobicity. Both the number and kind of microorganisms that colonize metal surfaces depend on the type of metal and the presence of an imposed electrical potential. No significant differences in attachment and growth of a pure culture were observed when metal surfaces were dipped in an exogenous energy source. The chemical composition of naturally occurring adsorbed organic films on metal surfaces was shown to be independent of surface composition and polarization [206].

There are several experimental evidences on bacterial attachment on Ti materials. Despite the wide use of dental implants, the understanding of the mechanisms of bacterial attachment to implant surfaces and of the factors that affect such attachment is limited. The attachment of oral bacteria, including *Streptococcus sanguis*, *Actinomyces viscosus*, and *Porphyromonas gingivalis*, to titanium discs with different surface morphology (smooth, grooved, or rough) was examined by SEM. The greatest bacterial attachment was observed on the rough BSA-coated

Ti surfaces (Bovine Serum Albumin, coated by 0.25 ml of 0.15% glycine—0.01% BSA at 4°C overnight). The smooth surfaces promoted poor attachment for *S. sanguis* and *A. viscosus*. However, *P. gingivalis* attached equally well to both the smooth and groove-coated Ti surfaces. Cell-surface fimbriae (which may play a role in adhesion) of both *A. viscosus* and *P. gingivalis* were observed to be associated with Ti surfaces. It was concluded that Ti surface characteristics appeared to influence oral bacteria attachment *in vitro* [207].

Steinberg et al. [208] investigated the adhesion of radioactively labeled *Actinomyces viscosus* (*A. viscosus*), *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*) and *P. gingivalis* to CpTi, Ti–6Al–4V coated with albumin or human saliva. It was reported that (i) all tested bacteria displayed greater attachment to Ti–6Al–4V than CpTi, (ii) *P. gingivalis* exhibited less adhesion to CpTi and Ti–6Al–4V than did the other bacterial strains, (iii) adhesion of *A. viscosus* and *A. actinomycetemcomitans* was greatly reduced when CpTi and Ti–6Al–4V were coated with albumin or saliva, and (iv) *P. gingivalis* demonstrated a lesser reduction in adhesion to albumin or saliva-coated surfaces. It was therefore suggested that oral bacteria have different adhesion affinities for CpTi and Ti–6Al–4V and that both albumin and human saliva reduce bacterial adhesion [208].

The adherence of *S. mutans* to six implant materials (polycrystal alumina, single crystal alumina, Ti–6Al–4V and Co–Cr–Mo alloy, hydroxyapatite HA, heat-curing PMMA resin) was studied *in vitro*. The change of free energy, which corresponds to the adherence process, was also evaluated for hydrophobic interaction. It was found that (i) adherence of *S. mutans* to polycrystal alumina was lower than adherence to other materials and (ii) the adherence of *S. mutans* to the test materials was highly correlated with the change of free energy, which suggests that hydrophobic interaction plays an important role in the adherence of *S. mutans* to the implant materials [209].

The relatively low toxicity and impressive biocompatibility of Ti in human tissues has favored its use as an implant material for the replacement of missing teeth [210]. The design of oral implants requires communication with the oral cavity through the mucosal or gingival tissues. Exposure in the mouth presents a unique surface that can interact with host indigenous bacteria, leading to plaque formation. Early colonization of the tooth surface starts by adhesion of salivary bacteria to the pellicle [211,212]. Plaque development on exposed surfaces of teeth and restoration materials begins with an acquired pellicle. The acquired pellicle consists primarily of glycoproteins, mucins, and enzymes present in saliva [213]. Electrostatic-type interaction between charged ions is one of the main routes in the formation of acquired pellicle on teeth and other materials. Thus, the greater quantities of salivary proteins adsorbing to enamel may be explained by the greater distribution of phosphate groups and calcium ions on enamel surfaces in relation to the Ti oxide layer. This results in a reduced affinity between Ti and charged salivary proteins [214,215]. After the adsorption of the proteins, bacteria begin to adhere to the acquired pellicle [216]. In the oral cavity, different adsorbed salivary proteins may dictate which oral bacteria first adhere and how the plaque will develop. Since Ti and enamel differ in their engagement of salivary components, the plaque

developing on a Ti surface and its potential pathogenicity may also differ [212]. Based on the above background, Leonhardt et al. [212] placed CpTi, HA (hydroxyapatite), and amalgam samples in Co–Cr splints and kept intraorally in each individual for 10 min, 1, 3, 6, 24 and 72 h. It was found that (i) qualitative or quantitative differences in early plaque formation were seen on the surfaces and (ii) the different kinds of materials did not seem to have any antibacterial properties *in vivo*, and it seems as if the adherent bacterial plaque had a similar composition, regardless of material [212]. Sordyl et al. [217] collected bacterial samples from the superior aspect of implants after bar and abutment were removed. They found that the plaque specimens contained a predominantly gram-positive microflora, although gram-negative species were present in low numbers [217]. Balkin et al. [218] examined the periimplant microbiota of human mandibular subperiosteal dental implants. The study established that gram-positive facultative *Streptococcus* and *Actinomyces* spp. are characteristic of subperiosteal implants with long-term clinical stability. Saleh et al. [219] studied the amount of plaque formation that occurs on CpTi, Ti–6Al–4V, gold, and enamel by using an artificial mouth system. *S. mutans* and *S. sanguis* were used as the test bacteria. The metals and control teeth were exposed to *S. mutans* for 2 days and *S. sanguis* for 3 days. It was reported that (i) a mean *S. mutans* coverage was 44% on the enamel, 98.5% on the gold, 91.8% on the CpTi, and 91.2% on the Ti–6Al–4V alloy, (ii) there was a statistically significant difference between enamel and the three metals, (iii) the mean of *S. sanguis* coverage was as follows: 48.3% on enamel, 50.4% on gold, 13% on CpTi, and 27.3% on Ti–6Al–4V alloy, and (iv) CpTi harbored less *S. sanguis* than enamel and gold, whereas enamel harbored less *S. mutans* than gold, CpTi, and Ti–6Al–4V alloy [219].

While there is considerable information about bacteria adhesion on enamel, little is known about the mechanism of bacterial interactions with implant materials in the oral cavity [208]. It was found that in edentulous mouths, the presence of gram-positive cocci around implants was significantly greater than that of other bacteria [220]. In partially edentulous, healthy, or diseased mouths, implants and teeth harbored the same type of bacteria [221,222]. No significant differences were found between the subgingival flora of teeth and titanium implants in an *in vivo* study [223] of a periodontally healthy mouth. Microbial plaque accumulation surrounding dental implants may develop into periimplantitis or periimplantoclasia, which is defined as inflammation or infection around an implant, with accompanying bone loss [224]. Periimplant disease can be as destructive as periodontal disease, and adequate diagnosis and timely treatment are essential. The microflora around successful implants is similar to healthy sulci, while that associated with failing implants is similar to periodontally diseased sites. Implant microflora is similar to the tooth microflora in the partially edentulous mouth. The microflora of implants in partially edentulous mouths differs from that in edentulous mouths. This seems to indicate a bacterial reservoir around the teeth and the possibility of reinfection of the implant sulcus by periodontal pathogens [225]. It is, therefore, important to maintain plaque-free surfaces on both supra- and sub-gingival portions of dental implants to prevent

preimplantitis. There are at least two methods of inhibiting the formation of microbial plaque. The first method is to inhibit the initial adhesion of oral bacteria. The second method is to inhibit the colonization of oral bacteria, which involves surface antibacterial activity. Yoshinari et al. [226] studied the antibacterial effect of surface modifications to Ti on *P. gingivalis* and *A. actinomycetemcomitans*. Surface modifications with the dry process included (1) ion implantation (Ca^+ , N^+ , F^+), (2) oxidation (anodic oxidation, titania spraying), (3) ion plating (TiN, alumina), and (4) ion beam mixing (Ag, Sn, Zn, Pt) with Ar^+ on CpTi plates. It was found that (i) F^+ -implanted specimens significantly inhibited the growth of both *P. gingivalis* and *A. actinomycetemcomitans* than the untreated Ti, (ii) the other surface-modified specimens did not exhibit effective antibacterial activity against both bacteria, and (iii) no release of fluoride ions were detected from F^+ -implanted specimens under dissolution tests. It was thus indicated that surface modifications by means of a dry process are useful in providing antibacterial activity of oral bacteria to Ti implants exposed to the oral cavity [226].

Both anaerobic and aerobic bacteria can participate in the process of microbiology-related corrosion. Sulfate-reducing bacteria are most prevalent under anaerobic conditions. Lekholm et al. [227] found that the microbial species around stable versus failing implants are similar to the patterns observed around healthy versus periodontally involved teeth. Quirynen and Listgarten [221] found no significant differences in the bacterial morphotypes between implants and natural teeth in partially edentulous patients (with implants and teeth in the same jaw). The percentages of coccoid cells, motile rods, spirochetes, and other bacteria were 65.8%, 2.3%, 2.1%, and 29.8% for implants and 55.6%, 4.9%, 3.6%, and 34.9% for teeth, respectively. The results suggested that teeth may serve as a reservoir for the bacterial colonization of Ti implants in the same mouth.

There exist several *in vitro* MIC-related corrosion tests. In an *in vitro* study using *S. epidermidis*, a slime-producing strain and its isogenic slime-negative mutant, it was found that (i) both strains adhere to CpTi discs with significantly higher colony counts for the slime-producing strain, (ii) the colony count was dependent on temperature, time, and stain, and (iii) slime production is important for adherence and subsequent accumulation of *S. epidermidis* onto CpTi discs *in vitro* [228]. Drake et al. [229] prepared CpTi surfaces by pretreating (SiC polished, sand blasted, 30% NHO_3 passivated), followed by exposing them to UV sterilization, steam autoclaving at 121°C , ethylene gas treatment at 55°C , and plasma cleaning in argon gas. These surface-modified CpTi were investigated in terms of wettability, roughness, mode of sterilization, and the ability of the oral bacterium *S. sanguis* to colonize. It was concluded that (i) Ti samples that exhibited rough or hydrophobic (low wettability) surfaces, along with all autoclaved surfaces, were preferentially colonized, (ii) Ti surfaces that had been repeatedly autoclaved were colonized with the levels of bacteria 3 to 4 orders of magnitude higher than other modes of sterilization, and (iii) this may have implications relative to the commonly used method of autoclaving titanium implants, which may ultimately enhance bacterial biofilm formation on these surfaces [229].

Bacterial reaction on teeth is different from that on titanium materials. Gibbons and Van Houte [211] noted that the interaction of host flora with teeth involves a highly selective process related to specific interactions between tooth-bound salivary pellicles and bacterial surface adhesions. The ion distribution and charge character of titanium should be different from enamel. Therefore, salivary pellicle formation at each of these surfaces may in turn be different. It was found that (i) using an *in vitro* adherence model significantly lowered numbers of *A. viscosus* bound to the salivary-treated Ti surface were found when compared to that of the similarly treated enamel, (ii) the binding of *S. sanguis* to Ti or enamel did not vary significantly, (iii) a comparison of the percentage of cells bound to the titanium surface revealed that *S. sanguis* cells attached in significantly higher numbers when compared to the *A. viscosus* cells, and (iv) formation of salivary protein pellicles on Ti may be quite different from that of enamel. It was further speculated that the changes seen in the pellicle formation are the result of an alteration in the rate of pellicle formation on Ti or the weakening of interactions of the salivary proteins with the surface, as a result of the lowered surface free energy [210], supporting observations by Fujioka-Hirai et al. [209].

Chang et al. [230] investigated electrochemical behaviors of CpTi, Ti–6Al–4V, NiTi, Co–Cr–Mo, 316L stainless steel, 17-4 PH stainless steel, and Ni–Cr in (1) sterilized Ringer's solution, (2) *S. mutans* mixed with sterilized Ringer's solution, (3) sterilized tryptic soy broth, and (4) byproduct of *S. mutans* mixed with sterilized tryptic soy broth. It was concluded that (i) among the four electrolytes, the byproduct mixed with sterilized tryptic soy broth was the most corrosive media, leading to an increase in I_{CORR} and reduction in E_{CORR} , (ii) CpTi, Co–Cr–Mo and stainless steel increased their I_{CORR} significantly, but Ti–6Al–4V and NiTi did not show remarkable increase in I_{CORR} [230].

Koh [177] studied the effect of surface area ratios on bacteria galvanic corrosion of CpTi coupled with other dental alloys. CpTi was coupled with a more noble metal (type IV dental gold alloy) and a less noble metal (Ni–Cr alloy) with different surface area ratios (ranging from 4:0 to 0:4—in other words, 4:0 uncouple indicates that entire surface area of a noble metal was masked, while 0:4 uncouple indicates that only CpTi surface was masked and area ratios between 4:0 and 0:4 indicate that both surfaces were partially masked to produce different surface areas). Galvanic couples were then electrochemically tested in bacteria culture media and culture media containing bacteria byproducts. It was found that I_{CORR} (and hence, corrosion rate) profiles as a function of surface area ratio showed a straight-line trend (meaning surface area ratio independence) for Ti/Au couples, whereas the representative curve for the Ti/Ni–Cr alloy was bowl shaped. The latter curve indicates further higher corrosion rates at both ends (larger area of either CpTi or Ni–Cr), meaning that the lowest corrosion rate was exhibited at the bottom of bowl (at equal surface area ratio) [177], supporting results obtained by Al-Ali et al. [178] and Garcia and Oshida [182].

Periprosthetic infections are considered difficult to treat because the biomaterial implant is ideal for bacterial adhesion and biofilm formation, which results in decreased antibiotic sensitivity [231]. The effect of Ti surface on *S. epidermidis*, a

Gram-positive organism prevalent in orthopedic infections, was investigated and concluded that antibiotic derivatization of implants can result in a surface that can resist bacterial colonization; this tendency holds great promise for the prevention and treatment of periprosthetic infections [231].

Since infection of an orthopedic prosthesis is undesirable and causes a decrease in the success rate of an implant, reducing the adhesion of a broad range of bacteria could be an attractive means to decrease infection and allow for subsequent appropriate tissue integration with the biomaterial surface [232]. Titanium surfaces with nanometer-sized textures were investigated for the adhesion of *S. aureus*, *S. epidermidis*, and *P. aeruginosa*. The conventional and nanorough Ti surfaces were found to have crystalline TiO₂, while the nanotubular and nanotextured Ti surfaces were amorphous. It was found that the nanorough Ti surfaces produced by electron beam evaporation decreased the adherence of bacteria and concluded that the result of the study demonstrated that certain nanometer-sized Ti topographies may be useful for reducing bacteria adhesion while promoting bone tissue formation and, thus, should be further studied for improving the efficacy of Ti-based orthopedic implants [232].

3.8 Reaction with Hydrogen

It is generally agreed that the solubility of hydrogen in α -phase titanium and titanium alloys is quite low, namely on the order of 20–2000 ppm at room temperature [233]. However, severe problems can arise when Ti-based alloys pick up large amounts of hydrogen, especially at elevated temperatures [234–238]. The strong stabilizing effect of hydrogen on the β phase field results in a decrease of α (HCP crystal structure) $\rightarrow$ β (BCC crystal structure) transformation temperature from 885°C to a eutectoid temperature of 300°C [234]. Hydrogen absorption from the surrounding environment leads to degradation of the mechanical properties of the material [239]. This phenomenon has been referred to as HE over the past years. Hydrogen absorption often becomes a problem for high-strength steels even in air [240], and it also occurs for Ti in methanol solutions containing hydrochloric acid [241–245]. Hydrogen damage of Ti and Ti-based alloys is manifested as a loss of ductility (embrittlement) and/or reduction in the stress intensity threshold for crack propagation [233]. CpTi is very resistant to HE, but it becomes susceptible to HE under an existence of notch, at low temperature, high-strain rates, or large grain sizes [246]. Eventually, all of these thermal and mechanical situations make the material more brittle in nature. For α and near α -Ti materials, it is believed that such HE occurs due to precipitation of brittle hydride phases [247]. For $\alpha + \beta$ phase alloys, when a significant amount of β phase is present, hydrogen can be preferentially transported with the β lattice and will react with α phase at α/β boundaries. Under this condition, degradation will generally become severe [248]. For β alloys, HE was observed to occur in the Ti–Mo–Nb–Al [249], Ti–V–Cr–Al–Sn [250], and Ti–V–Fe–Al alloys [251], due to δ -hydride phase formation, which is brittle at low temperatures [233].

It was confirmed that a shear crack initiated at the root of the thread and propagated into the inner section of the screw in the dental implant systems. Gas chromatography revealed that the retrieved screw absorbed a higher amount of hydrogen than the as-used CpTi sample. It was then suggested that CpTi in a biological environment absorbs hydrogen, and that this may be the reason for delayed fracture of Ti implants [240]. Such absorbed hydrogen might have two different sources. The first source of hydrogen is the internal hydrogen that is already present in the material, either in solution or as hydrides. The second source is external hydrogen, which is produced through the interaction between titanium and hydrogen or hydrogen-producing environments (including cathodic reaction during the corrosion reaction) during service. It is generally assumed that hydrogen from the environment is taken up by the titanium, thereby becoming internal hydrogen. Thus, the two effects are obviously very similar. As an alloying element in titanium, hydrogen provides very little increase in strength but can seriously impair both ductility and toughness [252–254].

There are some processes by which hydrogen could develop and possibly be absorbed under passive conditions: direct absorption of hydrogen produced by water hydrolysis and absorption of atomic hydrogen produced by the corrosion processes to produce an oxide. Under anodic conditions, when passive corrosion prevails, the corrosion potential for passive titanium must rise at a value at which water reduction can cause titanium to oxidize, $\text{Ti} + 2\text{H}_2\text{O} \rightarrow \text{TiO}_2 + 2\text{H}_2$. Since Ti hydrides are thermodynamically stable at these potentials, the passive film can only be considered as a transport barrier and not an absolute barrier. The rate of hydrogen absorption will be controlled by the rate of corrosion reaction, which dictates the rate of production of absorbable hydrogen. Since TiO_2 is extremely insoluble, the corrosion reaction will be effectively limited to an oxide film growth reaction [255]. Titanium corrosion processes are often accompanied by hydrogen production, introducing the possibility of the absorption of hydrogen into the material. Crevice corrosion, once initiated, is supported by both the reduction of oxygen on passive surfaces external to the crevice and the reduction of protons ($\text{Ti} + 4\text{H}^+ \rightarrow \text{Ti}^{4+} + 2\text{H}_2$) inside the crevice, leading to the absorption of atomic hydrogen in sufficient quantities to produce extensive hydride formation. For passive noncreviced or inert crevice conditions, corrosion could be sustained by reaction with water under neutral conditions ($\text{Ti} + 2\text{H}_2\text{O} \rightarrow \text{TiO}_2 + 2\text{H}_2$), and should proceed at an extremely slow rate. In the first step to possible failure by hydrogen-induced cracking, the hydrogen generated must pass through the TiO_2 film before absorption into the underlying titanium alloy. For absorption to proceed, redox transformation ($\text{Ti}^{4+} \rightarrow \text{Ti}^{3+}$) in the oxide film is necessary. This requires significant cathodic polarization of the metal, generally achievable by galvanic coupling to active materials (such as carbon steel), or by the application of cathodic protection potential [256].

Ogawa et al. [239] conducted immersion tests on a β Ti alloy (77.8Ti–11.3Mo–6.6Zr–4.3Sn) under sustained tensile load (0–900 MPa) for various periods at room temperature, in 0.2 and 2.0% APF (2% NaF + 1.7% H_3PO_4). Hydrogen absorption behavior in acid fluoride solution has been analyzed

by hydrogen thermal desorption. It was reported that (i) in the case of an immersion time of 60 h, the amount of absorbed hydrogen exceeded 10,000 ppm, while the amount of hydrogen absorbed in the 0.2% APF solution was several times smaller than that in 2% solution, (ii) for immersion in 0.2% APF, hydrogen absorption saturated after 48 h, and (iii) during the later stage of immersion, the amount of absorbed hydrogen markedly increased under higher applied stress, although the applied stress did not enhance hydrogen absorption during the early stage of immersion. These results of hydrogen absorption behavior are consistent with the delayed-fracture characteristics of the β Ti alloy [239].

Lane et al. [257] tested various Ti alloy cantilever beam specimens and reported that seawater embrittlement behavior is related to aluminum content, aging in the range of 480–700°C, and the presence of isomorphous β stabilizers (Mo, V, Co). Test results indicate that (i) seawater embrittlement is an environment-dependent brittleness triggered by an aqueous corrodent, (ii) seawater-sensitive Ti alloys include CpTi, Ti–7Al–2Nb–1Ta, Ti–7Al–3Nb, Ti–6Al–2.5Sn, and Ti–6Al–3Nb–2Sn, whereas seawater-insensitive Ti alloys include Ti–7Al–2.5Mo, Ti–6Al–2Sn–1Mo–1V, Ti–6.5Al–5Zr–1V, Ti–6Al–4V, and Ti–6Al–2Sn–1Mo–3V, and (iii) in order to reduce embrittlement, it is recommended to lower Al content and to add elements (Mo or V) that suppress the formation of coherent Ti₃Al [257].

Superelastic NiTi wire is widely used in orthodontic clinics, but delayed fracture in the oral cavity has been observed. Because HE is known to cause damage to Ti alloy systems, Yokoyama et al. [258] treated orthodontic wires cathodically in 0.9% NaCl solution for charging hydrogen followed by conducting tensile tests and fractographic observations. It was reported that (i) the strength of the Co–Cr alloy and stainless steel used in orthodontic mechano-treatment was not affected by the hydrogen charging; however, NiTi wire showed significant decreases in its strength and (ii) the fractured surface of the alloy with severe hydrogen charging exhibited dimple patterns similar to those in the alloys from patients. In view of the galvanic current in the mouth, the fracture of the NiTi alloy might be attributed to the degradation of the mechanical properties due to hydrogen absorption [258]. Hydrogen-induced embrittlement of NiTi was also found when it was tested in acidic solutions and fluoride-containing solutions such as APF [259,260]. However, it was suggested that the work-hardening NiTi alloy was less sensitive to HE compared with NiTi superelastic alloy [242].

Titanium reaction with hydrogen is not necessarily a useless phenomenon. The formation of titanium hydrides can provide an engineering advantage. It is well known that titanium is one of the most promising materials for hydrogen storage due to a stable formation of nonstoichiometric titanium hydrides (δ , ϵ , or γ type) such as the composition range from TiH_{1.53} to TiH_{1.99} [241].

Finally, the unique reaction of titanium with hydrogen can be used favorably for the grain refining, which has a sequence of hydrogen absorption→heat treatment and working→dehydrogen treatment. For example, Ti–3Al–2.5Sn containing 0.5 mass% of hydrogen was heated at 780°C and solid-solution treated, followed by water-quenched to have martensitic phase. The alloy was further subjected to hot-

rolling in the $\alpha + \beta$ dual structure, followed by heating at 600°C in vacuum to dehydrogen treatment [245]. Such treated Ti–3Al–2.5Sn shows a uniaxial microstructure with the grain size in a range from 0.5 to 1 μm , which is suitable for the superelastic forming.

References

- [1] Brockhurst PJ. Dental materials: new territories for materials science. In: Metals Forum. Australian Inst Metals 1980;3:200–10.
- [2] Hansen DC. Biological interactions at metal surfaces. J Met 2011;63:22–7.
- [3] Takemoto S, Hatori M, Yoshinari M, Kawada E, Oda Y. Corrosion behavior and surface characterization of titanium in solution containing fluoride and albumin. Biomaterials 2005;26:829–37.
- [4] Lausmaa J, Kasemo B, Hansson S. Accelerated oxide growth on titanium implants during autoclaving caused by fluorine contamination. Biomaterials 1985;6:23–7.
- [5] Wilhelmsen W, Grande AP. The influence of hydrofluoric acid and fluoride ion on the corrosion and passive behavior of titanium. Electrochim Acta 1987;32:1469–72.
- [6] Oda Y, Kawada E, Yoshinari M, Hsegawa K, Okabe T. The influence of fluoride concentration on the corrosion of titanium and titanium alloys. Dent Mater J 1996;15:317–22.
- [7] Nakagawa M, Matsuya S, Udoh K. Effect of fluoride and dissolved oxygen concentration on the corrosion behavior of pure titanium and titanium alloys. Dent Mater J 2002;21:83–92.
- [8] Harzer W, Schroter A, Gedrange T, Muschter F. Sensitivity of titanium brackets to the corrosive influence of fluoride-containing toothpaste and tea. Angle Orthod 2001;71:318–23.
- [9] Adell R, Lekholm U, Rockler B, Brånemark PIA. 15-year study of osseo-integrated implants in the treatment of the edentulous jaw. Int J Oral Surg 1981;10:387–416.
- [10] Bard JA. Titanium, vol. 5. New York, NY: Marcel Dekker; 1976. pp. 305–31
- [11] Barralis J, Meder G. *Precis de metallurgie, elaboration structurale, properties et normalisation*. Paris: Nathan; 1991. pp. 35–49
- [12] Watanabe I, Watanabe E. Surface changes induced by fluoride prophylactic agents on titanium-based orthodontic wires. Am J Orthod Dentofacial Orthop 2003;123:653–6.
- [13] Rosentritt M, Lang R, Plein T, Behr M, Handel G. Discoloration of restorative materials after bleaching application. Quint Int 2005;36:33–9.
- [14] Goldstein GR, Kiremidjian-Schuhmacher L. Bleaching: is it safe and effective? J Prosthet Dent 1993;69:325–8.
- [15] Attin T. The security and use of carbamide peroxide gels in bleaching therapy. Dtsch Zahnärztl Z 1998;53:11–6.
- [16] Haywood VB, Heymann HO. Nightguard vital bleaching: how safe is it? Quint Int 1991;22:515–23.
- [17] Dahl JE, Pallesen U. Tooth bleaching—a critical review of the biological aspects. Crit Rev Oral Biol Med 2003;14:292–304.
- [18] Oshida Y, Sellers CB, Mirza K, Farzin-Nia F. Corrosion of dental materials by dental treatment agents. Mater Sci Eng 2005;C25:343–8.
- [19] Albrektsson T. The response of bone to titanium implants. CRC Crit Rev Biocompatib 1985;1:53–84.

- [20] Noguchi T, Takemoto S, Hattori M, Yoshinari M, Kawada E, Oda Y. Discoloration and dissolution of titanium and titanium alloys with immersion in peroxide- or fluoride-containing solutions. *Dent Mater J* 2008;27:117–23.
- [21] Sellers CB, Oshida Y. Effects of fluoride treatment agents on dental metallic materials. AADR/IADR meeting, Honolulu HI; 2004 [Abstract No. 0066].
- [22] Boere G. Influence of fluoride on titanium in an acidic environment measured by polarization resistance technique. *J Appl Biomater* 1995;6:283–8.
- [23] Johansson BI, Bergman B. Corrosion of titanium and amalgam couples: effect of fluoride, area size, surface preparation and fabrication procedures. *Dent Mater* 1995;11:41–6.
- [24] Nakagawa M, Matsuya S, Shiraishi T, Ohta M. Effect of fluoride concentration and pH on corrosion behavior of titanium for dental use. *J Dent Res* 1999;78:1568–72.
- [25] Pröbster L, Kin W, Hüttermann H. Effect of fluoride prophylactic agents on titanium surfaces. *Int J Oral Maxillofac Implants* 1992;7:390–4.
- [26] Reclaru L, Meyer JM. Effects of fluorides on titanium and other dental alloys in dentistry. *Biomaterials* 1998;19:85–92.
- [27] Siirila HS, Kononen M. The effect of oral topical fluorides on the surface of commercially pure titanium. *Int J Oral Maxillofac Implants* 1991;6:50–4.
- [28] Thomas DE, Bomberger HB. The effect of chlorides and fluorides on titanium alloys in simulated scrubber environments. *Mater Perform* 1983;22:29–36.
- [29] Tounmelin-Chemla F, Rouelle F, Burdairon G. Corrosive properties of fluoride-containing odontological gels against titanium. *J Dent* 1996;24:109–15.
- [30] Schiff N, Grosogeat B, Lissac M, Dalard F. Influence of fluoridated mouth-washes on corrosion resistance of orthodontics wires. *Biomaterials* 2004;25:4535–42.
- [31] Mirza K, Oshida Y. Corrosiveness of bleaching agent on dental metallic materials. AADR/IADR meeting. Honolulu HI; 2004 [Abstract No. 0621].
- [32] Oshida Y, Mirza K, Sellers CB, Panyayong W, Farzin-Nia F. Effects of dental treatment agents on discoloration/corrosion behavior of metallic dental materials. In: Shrivastava S, editor. *Medical device materials*. Materials Park, OH: ASM International; 2004. p. 467–70.
- [33] Yoon SJ, Kim CW, Lim BS. Electrochemical corrosion of dental titanium in fluoride ion. *J Dent Res* 1997;76:81 [Abstract No. 538].
- [34] Matono Y, Nakagawa M, Matsuya S, Ishikawa K, Terada Y. Corrosion behavior of pure titanium and titanium alloys in various concentrations of acidulated phosphate fluoride (APF) solutions. *Dent Mater J* 2006;25:104–12.
- [35] Nakagawa M, Matono Y, Matsuya S, Udoh K, Ishikawa K. The effect of Pt and Pd alloying additions on the corrosion behavior of titanium in fluoride-containing environments. *Biomaterials* 2005;26:2239–46.
- [36] Kaneko K, Yokoyama K, Moriyama K, Asaoka K, Sakai J, Nahumo M. Delayed fracture of beta titanium orthodontic wire in fluoride aqueous solutions. *Biomaterials* 2003;24:2113–20.
- [37] Pan J, Liao H, Leygraf C, Thierry D, Li J. Variations of oxide films on titanium induced by osteoblast-like cell culture and the influence of an H₂O₂ pretreatment. *J Biomed Mater Res* 1998;40:244–56.
- [38] Mustafa K, Pan J, Wroblewski J, Leygraf C, Arvidson K. Electrochemical impedance spectroscopy and X-ray photoelectron spectroscopy analysis of titanium surfaces cultured with osteoblast-like cells derived from human mandibular bone. *J Biomed Mater Res* 2001;59:655–64.

- [39] Huang H-H. Effects of fluoride concentration and elastic tensile strain on the corrosion resistance of commercially pure titanium. *Biomaterials* 2002;23:59–63.
- [40] Yamazoe J, Nakagawa M, Matono Y, Takeuchi A, Ishikawa K. The development of Ti alloys for dental implant with high corrosion resistance and mechanical strength. *Dent Mater J* 2007;26:260–7.
- [41] Kumar S, Narayanan TS. Corrosion behavior of Ti–15Mo alloy for dental implant applications. *J Dent* 2008;36:500–7.
- [42] Matasa CG. Attachment corrosion and its testing. *J Clin Orthod* 1995;29:16–23.
- [43] Barton K. Protection against atmospheric corrosion. New York, NY: John Wiley & Sons; 1973. p. 202
- [44] Souza ME, Lima L, Lima CR, Zavaglia CA, Freire CM. Effects of pH on the electrochemical behaviour of titanium alloys for implant applications. *J Mater Sci Mater Med* 2009;20:549–52.
- [45] Nilner K, Holland RI. Electrochemical potentials of amalgam restorations in vivo. *Scand J Dent Res* 1985;93:357–9.
- [46] Corso PP, German RM, Simmons HD. Corrosion evaluation of gold-based dental alloys. *J Dent Res* 1985;64:854–9.
- [47] Reclaru L, Meyer JM. Zonal coulometric analysis of the corrosion resistance of dental alloys. *J Dent Res* 1995;23:301–11.
- [48] Ewers GJ, Thornber MR. The effect of a simulated environment on dental alloys. *J Dent Res* 1983;62:330 [Abstract No. 330].
- [49] Pourbaix M. Atlas of electrochemical equilibria in aqueous solutions. London: Pergamon Press; 1966.
- [50] Williams RL, Brown SA, Merritt K. Electrochemical studies on the influence of proteins on the corrosion of implant alloys. *Biomaterials* 1988;9:181–6.
- [51] Brown SA, Simpson JP. Crevice and fretting corrosion of stainless steel plates and screws. *J Biomed Mater Res* 1981;15:867–78.
- [52] Devine TM, Wulff J. Cast Sv wrought cobalt–chromium surgical implant alloys. *J Biomed Mater Res* 1975;9:151–67.
- [53] Lucas LC, Buchanan RA, Lemons JE, Griffin CD. Susceptibility of surgical cobalt-based alloys to pitting corrosion. *J Biomed Mater Res* 1982;16:799–810.
- [54] Man HC, Gabe DR. A study of pitting potentials for some austenitic stainless steels using a potentiodynamic technique. *Corr Sci* 1981;21:713–21.
- [55] Oshida Y, Sachdeva R, Mitazaki S. Microanalytical characterization and surface modification of NiTi orthodontic arch wires. *J Biomed Mater Eng* 1992;2:51–69.
- [56] Sherwin MP, Taylor DE, Waterhouse RB. An electrochemical investigation of fretting corrosion in stainless steel. *Corr Sci* 1971;11:419–29.
- [57] Bandy R, Cahoon JR. Effect of composition on the electrochemical behavior of austenitic stainless steel in Ringer's solution. *Corrosion* 1977;33:204–8.
- [58] Cahoon JR, Bandyopadhyaya R, Tennese L. The concept of protection potential applied to the corrosion of metallic orthopedic implants. *J Biomed Mater Res* 1975;9:259–64.
- [59] Cahoon JR, Chaturved MC, Tennese L. Corrosion studies on metallic implant materials. *J Assoc Ad Med Instrum* 1973;7:131–5.
- [60] Mueller HJ, Greener EH. Polarization studies of surgical materials in Ringer's solution. *J Biomed Mater Res* 1970;4:29–41.
- [61] Sutow EJ, Pollack SR, Korostoff A. An in vitro investigation of the anodic polarization and capacitance behavior of 316L stainless steel. *J Biomed Mater Res* 1976;10:671–93.

- [62] Syrett BC, Wing SS. Pitting resistance of new and conventional orthopaedic implants—effect of metallurgical conditions. *Corrosion* 1978;34:138–45.
- [63] Syrett BC, Wing SS. An electrochemical investigation of fretting corrosion of surgical implant materials. *Corrosion* 1978;34:379–86.
- [64] Hoar TP, Mears DC. Corrosion-resistant alloys in chloride solutions: materials for surgical implants. *Proc Royal Soc* 1966;294A:486–510.
- [65] Al-Ali S. Galvanic corrosion with and without crevice corrosion in titanium and dental precious alloy couples. Indiana University Master Thesis; 2002.
- [66] Dunigan-Miller J. Electrochemical corrosion behavior of commercially pure titanium materials fabricated by different methods in three electrolytes. Indiana University Master Thesis; 2004.
- [67] Alkhateeb E, Virtanen S. Influence of surface self-modification in Ringer's solution on the passive behavior of titanium. *J Biomed Mater Res* 2005;75A:934–40.
- [68] Steinemann S. Corrosion of surgical implants—in vivo and in vitro tests. In: Winters GD, Leray JL, deGroot K, editors. *Evaluation of biomaterials*. Chichester: John Wiley & Sons; 1980. pp. 1–34.
- [69] Revie RW, Greene ND. Comparison of the in vivo and in vitro corrosion of 18-8 stainless steel and titanium. *J Biomed Mater Res* 1969;3:465–70.
- [70] Colman RF, Herrington J, Scales JT. Concentration of wear products in hair, blood and urine after total hip replacement. *Br Med J* 1975;1:527–9.
- [71] Merritt K, Brown SA, Sharkey NA. Blood distribution of nickel, cobalt and chromium following intramuscular injection into hamsters. *J Biomed Mater Res* 1984;18:991–1004.
- [72] Samitz MH, Katz SA. Nickel dermatitis hazards from prostheses, in vivo and in vitro solubilization studies. *Br J Derm* 1975;92:287–90.
- [73] Williams DF, Askill IN. The adsorption and desorption of proteins on clean metal surfaces. *Trans Soc Biomater* 1983;6:119–21.
- [74] Williams DF, Clark GCF. The accelerated corrosion of pure metals by proteins. *Trans Soc Biomater* 1981;4:17–20.
- [75] Clark GCF, Williams DF. The effect of proteins on metallic corrosion. *J Biomed Mater Res* 1982;16:125–34.
- [76] Speck KM, Fraker AC. Anodic polarization behavior of Ti–Ni and Ti–6Al–4V in simulated physiological solutions. *J Dent Res* 1980;59:1590–5.
- [77] Brown SA, Merritt K. Electrochemical corrosion in saline and serum. *J Biomed Mater Res* 1980;14:173–5.
- [78] Poubaix M. Electrochemical corrosion of metallic biomaterials. *Biomaterials* 1984;5:122–34.
- [79] Pohrelyuk IM, Tkachuk OV, Proskurnyak RV. Corrosion resistance of the Ti–6Al–4V alloy with nitride coating in 0.9% NaCl. *J Met* 2011;63:35–40.
- [80] Mareci D, Chelariu R, Gordin DM, Ungureanu G, Gloriant T. Comparative corrosion study of Ti–Ta alloys for dental applications. *Acta Biomater* 2009;5:3625–39.
- [81] Kasemo B, Lausmaa J. Surface science aspects on inorganic biomaterials. *CRC Crit Rev Biocompatib* 1986;2:335–80.
- [82] Koike M, Fujii H. The corrosion resistance of pure titanium in inorganic acids. *Biomaterials* 2001;22:2931–6.
- [83] Merritt K, Rodrigo JJ. Immune response to synthetic materials, sensitization of patients receiving orthopaedic implants. *Clin Orthop* 1996;326:71–9.

- [84] Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoch M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am* 2000;82:457–76.
- [85] Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MAR. Sensitivity to titanium, a cause of implant failure? *Bone Joint Surg Br* 1991;73–B:25–8.
- [86] Abdallah HI, Balsara RK, O’Riordan AC. Pacemaker contact sensitivity: clinical recognition and management. *Ann Thorac Surg* 1994;57:1017–8.
- [87] Yamauchi R, Morita A, Tsuji T. Pacemaker dermatitis from titanium. *Contact Dermatitis* 2000;42:52–3.
- [88] Basketter DA, Whittle E, Monk B. Possible allergy to complex titanium salt. *Contact Dermatitis* 2000;42:310–1.
- [89] Simonis A, Krüämer A, Netuschil L, Schlachta T, Geis-Gerstorfer J. In-vivo-Korrosionsuntersuchungen am Zahnärztlichen Legierungen unter Berücksichtigung des Speichel-pH-Werts. *Dtsch Zahnärztl Z* 1990;45:485–90.
- [90] Suga S, editor. *Illustrated cardiology*. Tokyo: Ishiyaku Publishers; 1990. p. 120–127
- [91] Ravnholt G. Corrosion current and pH rise around titanium coupled to dental alloys. *Scand J Dent Res* 1988;96:466–72.
- [92] Imfeld T. Evaluation of the cariogenicity of confectionery by intra-oral wire-telemetry. *Schweiz Monatsschr Zahnheilkd* 1977;87:437–64.
- [93] Miura I, Ida K, editors. *Dental uses of titanium*. Tokyo: Quintessence Book; 1988.
- [94] Gluszek J, Jędrkowiak J, Markowski J, Masalski J. Galvanic couples of 316L steel with Ti and ion plated Ti and TiN coatings in Ringer’s solutions. *Biomaterials* 1990;11:330–5.
- [95] Hernandez FE. Corrosion behavior of commercially pure titanium with different grades and from different material suppliers. *Indiana University Master Thesis*; 2003.
- [96] Kuphasuk C, Oshida Y, Andres CJ, Hivijitra ST, Barco MT, Brown DT. Electrochemical corrosion of titanium and titanium-based alloys. *J Prosthet Dent* 2001;85:195–202.
- [97] Güleriyüz H, Çimenoglu H. Effect of thermal oxidation on corrosion and corrosion-wear behaviour of a Ti–6Al–4V alloy. *Biomaterials* 2004;25:3325–33.
- [98] Starosvetsky D, Gotman I. Corrosion behavior of titanium nitride coated Ni–Ti shape memory surgical alloy. *Biomaterials* 2001;22:1853–9.
- [99] Huang H-H. Corrosion resistance of stressed NiTi and stainless steel orthodontic wires in acid artificial saliva. *J Biomed Mater Res* 2003;66A:829–39.
- [100] Carroll WM, Kelly MJ. Corrosion behavior of nitinol wires in body fluid environments. *J Biomed Mater Res* 2003;67A:1123–30.
- [101] Huang H-H. Surface characterizations and corrosion resistance of nickel–titanium orthodontic archwires in artificial saliva of various degrees of acidity. *J Biomed Mater Res* 2005;74A:629–39.
- [102] Tan L, Dodd RA, Crone WC. Corrosion and wear-corrosion behavior of NiTi modified by plasma source ion implantation. *Biomaterials* 2003;24:3931–9.
- [103] Stone P, Bennett RA, Bowker M. Reactive re-oxidation of reduced TiO₂(110) surfaces demonstrated by high temperature STM movies. *New J Phys* 1999;1:1–12.
- [104] Hanawa T, Ota M. Calcium phosphate naturally formed on titanium in electrolyte solution. *Biomaterials* 1991;12:767–76.
- [105] Demri B, Hage-Ali M, Moritz M, Muster D. Surface characterization of C/Ti 6Al 4V coating treated with ion beam. *Biomaterials* 1997;18:305–10.

- [106] Green SM, Grant DM, Wood JV, Johanson A, Johnson E, Sarholt-Kristensen L. Effect of N^+ implantation on the shape memory behavior and corrosion resistance of an equiatomic NiTi alloy. *J Mater Sci Lett* 1993;12:618–9.
- [107] Chen J, Conrad JR, Dodd RA. Methane plasma source ion implantation (PSII) for improvement of tribological and corrosion properties. *J Mater Process Technol* 1995;49:115–24.
- [108] Riviere JP. Formation of hard coatings for tribological and corrosion protection by dynamic ion mixing. *Surf Coat Technol* 1998;108:276–83.
- [109] Mandl S, Krause D, Thorwarth G, Sader R, Zeilhofer F, Horch HH, et al. Plasma immersion ion implantation treatment of medical implants. *Surf Coat Technol* 2001;142:1046–50.
- [110] Rondelli G. Corrosion resistance tests on NiTi shape memory alloy. *Biomaterials* 1996;17:2003–8.
- [111] Iijima M, Endo K, Ohno H, Mizoguchi I. Effect of Cr and Cu addition on corrosion behavior of Ni–Ti alloys. *Dent Mater J* 1998;17:31–40.
- [112] ASTM F 746-87 Standard Test method for pitting or crevice corrosion of metallic surgical implant materials. In: Annual book of ASTM standards, vol. 13.01. Philadelphia, PA: American Society for Testing and Materials; 1996. pp. 80–5.
- [113] Rondelli G, Vicentini B. Effect of copper on the localized corrosion resistance of Ni–Ti shape memory alloy. *Biomaterials* 2002;23:639–44.
- [114] Oliveira NTC, Biaggio SR, Rocha-Filho RC, Bocchi N. Electrochemical studies on zirconium and its biocompatible alloys Ti–50Zr at.% and Zr–2.5Nb wt.% in simulated physiologic media. *J Biomed Mater Res* 2005;74A:397–407.
- [115] Fox WC, Miller MA. Osseous implant for studies of biomaterials using an in vivo electrochemical transducer. *J Biomed Mater Res* 1993;27:763–73.
- [116] Aziz-Kerrzo M, Conroy KG, Fenelon AM, Farrell AT, Breslin CB. Electro-chemical studies on the stability and corrosion resistance of titanium-based implant materials. *Biomaterials* 2001;22:1531–9.
- [117] Khan MA, Williams RL, Williams DF. The corrosion behaviour of Ti–6Al–4V, Ti–6Al–7Nb and Ti–13Nb–13Zr in protein solutions. *Biomaterials* 1999;20:631–7.
- [118] Khan MA, Williams RL, Williams DF. Conjoint corrosion and wear in titanium alloy. *Biomaterials* 1999;20:765–72.
- [119] Merritt K, Brown SA. Biological effect of corrosion products from metals. ASTM STP 859. In: Fraker AC, Griffin CD, editors. Corrosion and degradation of implant materials: Second symposium; 1985. pp. 195–207.
- [120] Khan MA, Williams RL, Williams DF. In-vitro corrosion and wear of titanium alloys in the biological environment. *Biomaterials* 1996;17:2117–26.
- [121] Goodman SB, Davidson JA, Song Y, Martial N, Fornasier VL. Histo-morphological reaction of bone to different concentrations of phagocytosable particles of high-density polyethylene and Ti–6Al–4V alloy in vivo. *Biomaterials* 1996;17:1943–7.
- [122] Ebara R, Yamada Y, Goto A. Corrosion-fatigue behavior of Ti–6Al–4V in a sodium chloride aqueous solution ASTM STP In: Crooker TW, Leis BN, editors. Corrosion fatigue: mechanics, metallurgy, electrochemistry, and engineering, 801. Philadelphia, PA: American Society for Testing and Materials; 1983. pp. 135–46.
- [123] Zavanelli RA, Pessanha GE, Ferreira I, de A, Rollo JMD. Corrosion-fatigue life of commercially pure titanium and Ti–6Al–4V alloys in different storage environments. *J Prosthet Dent* 2000;84:274–9.

- [124] Ntasi A, Mueller WD, Eliades G, Zinelis S. The effects of Electro Discharge Machining (EDM) on the corrosion resistance of dental alloys. *Dent Mater* 2010;26:237–45.
- [125] Yu WQ, Qiu J, Xu L, Zhang FQ. Corrosion behaviors of TiO₂ nanotube layers on titanium in Hank's solution. *Biomed Mater* 2009;4:065012–8.
- [126] Popa MV, Demetrescu I, Suh SH, Vasilescu E, Drob P, Ionita D, et al. Monitoring of titanium base alloys–biofluids interface. *Bioelectrochemistry* 2007;71:126–34.
- [127] Popa MV, Vasilescu E, Drob P, Vasilescu C, Demetrescu I, Ionita D. Long-term assessment of the implant titanium material-artificial saliva interface. *J Mater Sci Mater Med* 2008;19:1–9.
- [128] Williams DF. The properties of titanium and its uses in cardiovascular surgery. *J Cardiovasc Technol* 1978;20:52–65.
- [129] Brune D. Metal release from dental biomaterials. *Biomaterials* 1986;7:163–75.
- [130] Brown SA, Merritt K, Farnsworth LJ, Crowe TD. Biological significance of metal ion release ASTM STP 953 In: Lemonds JE, editor. Quantitative characterization and performance of porous implants for hard tissue applications. Conshohocken: PA, USA. American Society for Testing and Materials; 1987. pp. 163–81
- [131] Van Orden AC, Fraker AC, Sung P. The influence of small variations in composition on the corrosion of cobalt-chromium alloys. *Proc Soc Biomater* 1982;5:108–12.
- [132] Meachim G, Williams DF. Tissue changes adjacent to titanium implants. *J Biomed Mater Res* 1973;7:555–72.
- [133] Woodman JL, Jacobs JJ, Galante JO, Urban RM. Metal ion release from titanium-based prosthetic segmental replacements of long bones in baboons: a long-term study. *J Orthop Res* 1984;1:421–30.
- [134] Bundy KJ, Williams CJ, Luedemann RE. Stress-enhanced ion release—the effect of static loading. *Biomaterials* 1991;12:627–39.
- [135] Cortada M, Giner L, Costa S, Gil FJ, Rodríguez D, Planell JA. Metallic ion release in artificial saliva to titanium oral implants coupled with different superstructures. *J Biomed Mater Eng* 1997;7:213–20.
- [136] Goyer RA. Toxic effects of metals. In: Klaassen CD, Amdur MO, Doull J, editors. Cassarett and Doull's toxicology. New York, NY: Macmillan; 1986. pp. 582–635.
- [137] Beach JD. Nickel carbonyl inhibition of RNA synthesis by a chromatin–RNA polymerase complex from hepatitic nuclei. *Cancer Res* 1970;30:48–50.
- [138] Stenborg T. Release of cobalt from cobalt–chromium alloy constructions in the oral cavity of man. *Scand J Dent Res* 1982;90:472–9.
- [139] P. Rechmann. LAMMS and ICP-MS detection of dental metallic compounds in non-discolored human gingival. *Dent Res* 1992;71:599–603.
- [140] Hao SQ, Lemons JE. Histology of dog dental tissues with Cu-based crowns. *Dent Res* 1989;68:322–7.
- [141] Okazaki Y, Gotoh E. Comparison of metal release from various metallic biomaterials in vitro. *Biomaterials* 2005;26:11–21.
- [142] Burstein GT, Liu C, Souto RM. The effect of temperature on the nucleation of corrosion pits on titanium in Ringer's physiological solution. *Biomaterials* 2005;26:245–56.
- [143] Ong JL, Lucas LC, Raikar KN, Gregory JC. Electrochemical corrosion analyses and characterization of surface-modified titanium. *Appl Surf Sci* 1993;72:7–13.
- [144] Okazaki Y, Nishimura E, Nakada H, Kobayashi K. Surface analysis of Ti–15Zr–4Nb–4Ta alloy after implantation in rat tibia. *Biomaterials* 2001;22:599–607.

- [145] Heusler KE. The influence of electrolyte composition on the formation and dissolution of passivating films. *Corr Sci* 1989;29:131–47.
- [146] Chang E, Lee TM. Effect of surface chemistries and characteristics of Ti6Al4V on the Ca and P adsorption and ion dissolution in Hank's ethylene diamine tetra-acetic acid solution. *Biomaterials* 2002;23:2917–25.
- [147] Wisbey A, Gregson PJ, Peter LM, Tuke M. Effect of surface treatment on the dissolution of titanium-based implant materials. *Biomaterials* 1991;12:470–3.
- [148] Healy KE, Ducheyne P. The mechanisms of passive dissolution of titanium in a model physiological environment. *J Biomed Mater Res* 1992;26:319–38.
- [149] Okazaki Y. Effect of friction on anodic polarization properties of metallic biomaterials. *Biomaterials* 2002;93:2071–7.
- [150] Oshida Y, Farzin-Nia F, Ito M, Panyaypong W. Passivation stability of titanium. In: Helmus M, Medlin D, editors. *Medical device materials II*. Materials Park, OH: ASM International; 2005. pp. 375–9.
- [151] Solar RJ, Pollack SR, Korostoff E. Titanium release from implants: a proposed mechanism. *Corrosion and degradation of implant materials*. Kansas City, MO: Symp American Society for Testing and Materials; 1978. pp. 2–3.
- [152] Woodman JR, Jacobs JJ, Galante JO, Urban RM. Titanium release from fiber metal compositions in baboons—a long term study. *Trans Orthop Res Soc* 1982;7:166–71.
- [153] Woodman JR, Jacobs JJ, Urban RM, Galante JO. Vanadium and aluminum release from fiber metal composites in baboons—a long term study. *Trans Orthop Res Soc* 1983;8:238–43.
- [154] Ducheyne P, Willems G, Martens M, Helsen L. In vivo metal-ion release from porous titanium-fiber material. *J Biomed Mater Res* 1984;18:293–308.
- [155] Strietzel R, Hösch A, Kalbfleisch H, Buch D. In vitro corrosion of titanium. *Biomaterials* 1998;19:1495–9.
- [156] Boths SJ, Coetzee WJC. Metal leaching from the Ti_2O_3 surfaces of different Ti-metals. *J Dent Res, Spec Iss* 1996;75:75 [Abstract No. 460].
- [157] Thompson GJ, Puleo DA. Ti–6Al–4V ion solution inhibition of osteogenic cell phenotype as a function of differentiation timecourse in vitro. *Biomaterials* 1996;17:1949–54.
- [158] Betts F, Wright T, Salvati EA, Boskey A, Bansal M. Cobalt-alloy metal debris in periarthritic tissues from total hip revision arthroplasties. *Clin Orthop* 1992;276:75–82.
- [159] Margevicius KJ, Bauer T, McMahan JT, Brown SA, Merritt K. Isolation and characterization of debris in membranes around total hip prostheses. *J Bone Joint Surg* 1994;76-A:1664–75.
- [160] Dorr LD, Bloebaum R, Emmanual J, Meldrum R. Histologic, biochemical, and ion analysis of tissue and fluids retrieved during total hip arthroplasty. *Clin Orthop* 1990;261:82–95.
- [161] Henning FF, Raithel HJ, Schaller KH, Döhler JR. Nickel-chrome- and cobalt-concentrations in human tissue and body fluids of hip prosthesis patients. *J Trace Elem Electrolytes Health Dis* 1992;6:239–43.
- [162] Thompson GJ, Puleo DA. Effects of sub-lethal metal ion concentrations on osteogenic cells derived from bone marrow stromal cells. *J Appl Biomater* 1995;6:249–58.
- [163] Park HY, Shearer TR. In vitro release of nickel and chromium from simulated orthodontic appliances. *Am J Orthod* 1983;84:156–9.
- [164] Kerosuo H, Moe G, Kleven E. In vitro release of nickel and chromium from different types of simulated orthodontic appliances. *Angle Orthod* 1995;65:111–6.

- [165] Kimura H, Sohmura T. Improvement in corrosion resistance of Ti–Ni shape memory alloy by oxide film coating. *Jpn J Dent Mater* 1988;7:106–10.
- [166] Huang H-H, Chiu Y-H, Lee T-H, Wu S-C, Yang H-W, Su K-H, et al. Ion release from NiTi orthodontic wires in artificial saliva with various acidities. *Biomaterials* 2003;24:3585–92.
- [167] Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978;98:197–201.
- [168] Schroeder HA, Balassa JJ, Tipton IH. Abnormal trace metals in man—nickel. *J Chronic Dis* 1962;15:51–62.
- [169] Black J. Systemic effects of biomaterials. *Biomaterials* 1984;5:11–8.
- [170] Johansson C, Lausmaa J, Ask M, Hansson HA, Albrektsson T. Ultrastructural differences of the interface zone between bone and Ti–6Al–4V or commercially pure titanium. *J Biomed Eng* 1989;111:3–8.
- [171] Wisbey A, Gregson PJ, Peter LM, Tuke M. Titanium release from TiN coated implant materials. International conference on changing role of engineering in orthopedics (MEP). London, UK; 1989. pp. 9–14.
- [172] Spriano S, Bosetti M, Bronzoni M, Vernè E, Maina G, Bergo V, et al. Surface properties and cell response of low metal ion release Ti–6Al–7Nb alloy after multi-step chemical and thermal treatments. *Biomaterials* 2005;26:1219–29.
- [173] Sarmiento-González A, Encinar JR, Marchante-Gayón JM, Sanz-Medel A. Titanium levels in the organs and blood of rats with a titanium implant, in the absence of wear, as determined by double-focusing ICP-MS. *Anal Bioanal Chem* 2009;393:335–43.
- [174] Wranglén G. An introduction to corrosion and protection of metals. New York, NY: Chapman & Hall; 1985. pp. 85–87
- [175] Van Black LH. Elements of materials science and engineering. Reading, MA: Addison-Wesley; 1989. pp. 509–511
- [176] Garcia I. Galvanic corrosion of dental implant materials. Indiana University Master Degree Thesis; 2000.
- [177] Koh II-W. Effects of bacteria-induced corrosion on galvanic couples of commercially pure titanium with other dental alloys. Indiana University Mater Degree Thesis; 2003.
- [178] Al-Ali S, Oshida Y, Andres CJ, Barco MT, Brown DT, Hovijitra S, et al. Effects of coupling methods on galvanic corrosion behavior of commercially pure titanium with dental precious alloys. *J Biomed Mater Eng* 2005;15:307–16.
- [179] Fontana MG, Greene ND. Corrosion Engineering. New York, NY: McGraw-Hill; 1967. pp. 20–5 and 330–8
- [180] Tomashov ND. Theory of corrosion and protection of metals. New York, NY: MacMillan; 1966. pp. 212–8
- [181] Uhlig HH, Revie RW. Corrosion and corrosion control. New York, NY: John Wiley & Sons; 1985. pp. 101–5
- [182] Garcia I, Oshida Y. Surface area ratio effects on galvanic corrosion of titanium couples. *J Dent Res* 2001;80 [Abstract No. 798].
- [183] American society for testing and materials: standard guide for development and used of galvanic series for predicting galvanic corrosion performance. vol. 03.02; 1991. pp. 334–40.
- [184] Johansson BI, Lucas LC, Lemons JE. Corrosion of copper, nickel, and gold dental casting alloys: an in vitro and in vivo study. *J Biomed Mater Res* 1989;23:349–61.
- [185] Lemons JE. Dental implant retrieved analyses. In: Risso AA, editor. Proceeding of the 1988 consensus development conference on dental implants. *J Dent Res* 1988;748–56.

- [186] Venugopalan R, Lucas LC. Evaluation of restorative and implant alloys galvanically coupled to titanium. *Dent Mater* 1998;14:165–72.
- [187] Leinfelde KF, Lemons JE. Clinical restorative materials and techniques. Philadelphia, PA: Lea & Febiger; 1988. pp. 139–59.
- [188] Lucas LC, Lemons JE. Biodegradation of restorative metallic systems. *Adv Dent Res* 1992;6:32–7.
- [189] Silver IA, Murrills RJ, Etherington DJ. Microelectrode studies on the acid microenvironment beneath adherent macrophages and osteoclasts. *Exp Cell Res* 1988;175:266–76.
- [190] Bagambiosa FB, Joos U, Schilli W. Interaction of osteogenic cells with hydroxylapatite implant materials in vitro and in vivo. *Int J Oral Maxillofac Implants* 1990;5:217–26.
- [191] Blair HC, Teitelbaum SL, Tan HL, Koziol CM, Schlesinger PH. Passive chloride permeability charge coupled to (H^+) -ATPase of avian osteoclast ruffled membrane. *Am J Phys* 1991;260:1315–9.
- [192] Bundy K, Laycock Y, Gomez-Novoa C, Bucalo V. Mechanisms of surface attack of molecular THR: a study of galvanic contact and crevice conditions. Proceedings of the symposium on compatibility of biomedical implants, vol. 94-15. Electrochemical Society; 1994. pp. 307–18.
- [193] Uhlig HH. Corrosion control. New York, NY: John Wiley & Sons; 1965. pp. 92–6.
- [194] Grosogeat B, Reclaru L, Lissac M, Dalard F. Measurement and evaluation of galvanic corrosion between titanium/Ti6Al4V implants and dental alloys by electrochemical techniques and auger spectroscopy. *Biomaterials* 1999;20:933–41.
- [195] Yamazoe M. Study of corrosion of combinations of titanium/Ti–6Al–4V implants and dental alloys. *Dent Mater J* 2010;29:542–53.
- [196] Tiller AK. Aspects of microbial corrosion. In: Parkins RN, editor. Corrosion processes. London: Applied Science; 1982. pp. 115–9.
- [197] Matasa CG. Stainless steels and direct-bonding brackets, III: microbiological properties. *Inf Orthod Kieferorthop* 1993;25:269–71.
- [198] Mansfeld F, Little BJ. A technical review of electrochemically techniques applied to microbiologically influenced corrosion. *Corr Sci* 1991;32:247–72.
- [199] Dexter SC, Duquette DJ, Siebert OW, Videla HA. Use and limitations of electrochemical techniques for investigation microbiological corrosion. *Corrosion* 1991;47:308–18.
- [200] Pope DH, Stoecker JG. Microbiologically influenced corrosion. Proceedings Industries Corrosion NACE. 1986. p. 235.
- [201] Walsh D, Pope D, Danford M, Huff T. The effect of microstructure on microbiologically influenced corrosion. *J Met* 1993;45:22–30.
- [202] Dexter SC. Microbiological effects. In: Baboian R, editor. Corrosion tests and standards: application and interpretation, 20. ASTM Manual Series MNL; 1995. pp. 419–29.
- [203] Gibbons RJ, Cohen L, Hay DI. Strains of *Streptococcus mutans* and *Streptococcus sobrinus* attach to different pellicle receptors. *Infect Immun* 1986;52:555–61.
- [204] An YH, Friedman RJ. Concise review of mechanisms of bacterial adhesion to biomaterial surfaces. *J Biomed Mater Res* 1998;43:338–48.
- [205] Tsibouklis J, Stone M, Thorpe AA, Graham P, Peters V, Heerlien R, et al. Preventing bacterial adhesion onto surfaces: the low-surface-energy approach. *Biomaterials* 1999;20:1229–35.

- [206] Little BJ, Wagner P. Factors influencing the adhesion of microorganism to surfaces. *J Adhes* 1986;20:187–210.
- [207] Wu-Yuan CD, Eganhouse KJ, Keller JC, Walters KS. Oral bacterial attachment to titanium surfaces: a scanning electron microscopy study. *J Oral Implant* 1995;21:207–13.
- [208] Steinberg D, Sela MN, Klinger A, Kohavi D. Adhesion of periodontal bacteria to titanium, and titanium alloy powders. *Clin Oral Implant Res* 1998;9:67–72.
- [209] Fujioka-Hirai Y, Akagawa Y, Minagi S, Tsuru H, Miyake Y, Sugunaka H. Adherence of *Streptococcus mutans* to implant materials. *J Biomed Mater Res* 1987;21:913–20.
- [210] Wolinsky LE, de Camargo PM, Erard JC, Newman MG. A study of in vitro attachment of *Streptococcus sanguis* and *Actinomyces viscosus* to saliva-treated titanium. *Int J Oral Maxillofac Implants* 1989;4:27–31.
- [211] Gibbons RJ, Van Houte J. Bacterial adherence and the formation of dental plaques. In: Beachey EH, editor. *Bacterial adherence*. New York, NY: Chapman & Hall; 1980. p. 61–104.
- [212] Leonhardt Å, Olsson J, Dahlén G. Bacterial colonization on titanium, hydroxyl-apatite, and amalgam surfaces in vivo. *J Dent Res* 1995;74:1607–12.
- [213] Kohavi D, Klinger A, Steinberg D, Sela MN. Adsorption of salivary proteins onto prosthetic titanium components. *J Prosthet Dent* 1995;74:531–4.
- [214] Rolla G. Formation of dental integuments—some basic chemical considerations. *Swed Dent J* 1977;1:241–51.
- [215] Kasemo B. Biocompatibility of titanium implants: surface science aspects. *J Prosthet Dent* 1983;49:832–7.
- [216] Kolenbrander PE, London J. Adhere today, here tomorrow: oral bacterial adherence. *J Bacteriol* 1993;175:3247–52.
- [217] Sordyl CM, Simons AM, Molinari JA. The microbial flora associated with stable endosseous implants. *J Oral Implant* 1995;21:19–22.
- [218] Balkin BE, Robert TW, Feik D, Molzan AK, Ram TE. Microbiology of human mandibular subperiosteal dental implants in healthy and disease. *J Dent Res* 2000;79:168 [Abstract No. 195].
- [219] Al Saleh KA, Simonsson T, Nilner K, Bondsson HE. Plaque formation on titanium, in vitro study. *J Dent Res* 1994;78:374 [Abstract No. 2174].
- [220] Mombelli A, Buser D, Lang NP. Colonization of osseointegrated titanium implants in edentulous patients. Early results. *Oral Microbiol Immunol* 1988;3:113–20.
- [221] Quirynen M, Listgarten M. Distribution of bacterial morphotypes around natural teeth and titanium implant of modum Branemark. *Clin Oral Implant Res* 1990;1:8–13.
- [222] Apse P, Ellen RP, Overall CM, Zarb GA. Microbiota and crevicular fluid collagenase activity in the osseointegrated dental implant sulcus: a comparison of sites in edentulous and partially edentulous patients. *J Periodont Res* 1989;24:96–105.
- [223] Kohavi D, Greenberg R, Raviv E, Sela MN. Sub- and supragingival microbial flora around healthy osseointegrated implants in partially edentulous patients. *Int J Oral Maxillofac Implants* 1994;9:673–8.
- [224] Haanaes HR. Implants and infections with special reference to oral bacteria. *J Clin Periodontol* 1990;17:516–24.
- [225] Bauman GR, Mills M, Rapley JW, Hallmon WW. Plaque-induced inflammation around implants. *Int J Oral Maxillofac Implants* 1992;7:330–7.
- [226] Yoshinari M, Oda Y, Kato T, Okuda K. Influence of surface modifications to titanium on antibacterial activity in vitro. *Biomaterials* 2001;22:2043–8.

- [227] Lekholm U, Ericsson I, Adell R, Slots J. The condition of the soft tissues at tooth and fixture abutment supporting fixed bridges, a microbiological and histological study. *J Clin Periodont* 1986;13:558–62.
- [228] König DP, Perdreau-Remington F, Rütt J, Stoßberger P, Hilgers R-D, Plum G. Slime production of *Staphylococcus epidermidis*; increased bacterial adherence and accumulation onto pure titanium. *Acta Orthop Scand* 1998;69:523–6.
- [229] Drake DR, Paul J, Keller JC. Primary bacterial colonization of implant surfaces. *Int J Oral Maxillofac Implants* 1999;14:226–32.
- [230] Chang J-C, Oshida Y, Gregory RL, Andres CJ, Barco TM, Brown DT. Electro-chemical study on microbiology-related corrosion of metallic dental materials. *J Biomed Mater Eng* 2003;13:281–95.
- [231] Antoci V, Adams CS, Parvizi J, Davidson HM, Composto RJ, Freeman TA, et al. The inhibition of *Staphylococcus epidermidis* biofilm formation by vancomycin-modified titanium alloy and implications for the treatment of periprosthetic infection. *Biomaterials* 2008;29:4684–90.
- [232] Puckett SD, Taylor E, Raimondo T, Webster TJ. The relationship between the nanostructure of titanium surfaces and bacterial attachment. *Biomaterials* 2010;31:706–13.
- [233] Moodey NR, Costa JE. In: Kim YW, Boyer RR, editors. *Microstructure/property relationship in titanium alloys and titanium aluminides*. Warrendale, PA: TMS; 1991. p. 587–604.
- [234] Tal-Gutelmacher E, Eliezer D. The hydrogen embrittlement of titanium-based alloys. *J Met* 2005;57:46–9.
- [235] Williams DN, Jaffee RI. Relationships between impact and low-strain-rate hydrogen embrittlement of titanium alloys. *J Less Common Met* 1960;2:42–8.
- [236] Hardie D, Quyang S. Effect of hydrogen and strain rate upon the ductility of mill-annealed Ti6Al4V. *Corr Sci* 1999;41:155–77.
- [237] Solovioff G, Eliezer D, Desch PB, Schwarz RB. Hydrogen-induced cracking in an Al–Al₃Ti–Al₄C₃ alloy. *Scr Metall Mater* 1995;33:1315–20.
- [238] Froes FH, Eliezer D, Nelson HG. In: Thompson AW, Moody NR, editors. *Hydrogen effects in materials*. Warrendale, PA: TMS; 1994. pp. 719–33.
- [239] Ogawa T, Yokoyama K, Asaoka K, Sakai J. Hydrogen absorption behavior of beta titanium alloy in acid fluoride solutions. *Biomaterials* 2004;25:2419–25.
- [240] Hirth JP. Effects of hydrogen on the properties of iron and steel. *Metall Trans A* 1980;11A:861–90.
- [241] Yokoyama K, Kaneko K, Ogawa T, Moriyama K, Asaoka K, Sakai J. Hydrogen embrittlement of work-hardened Ni–Ti alloy in fluoride solutions. *Biomaterials* 2005;26:101–8.
- [242] Paton NE, Williams LC. *Effect of hydrogen on titanium and its alloys*. Hydrogen in metals. Cleveland, OH: American Society for Metals; 1974. p. 409–32.
- [243] Ebtehaj K, Hardie D, Parkins RN. The stress corrosion and pre-exposure embrittlement of titanium in methanolic solutions of hydrochloric acid. *Corr Sci* 1985;25:415–29.
- [244] Hollis AC, Scully JC. The stress corrosion cracking and hydrogen embrittlement of titanium in methanol–hydrochloric acid solutions. *Corr Sci* 1993;34:821–35.
- [245] Nakahigashi J, Tsuru K, Yoshimura H. Application of hydrogen-treated titanium alloy to dental prosthesis. Experimental manufacture of crown by superplastic forming. *J Jpn Soc Dental Mater Devices* 2005;24:291–5.
- [246] Gerard DA, Koss DA. The combined effect of stress state and grain size on hydrogen embrittlement of titanium. *Scr Met Mater* 1985;19:1521–4.

- [247] Shih DS, Robertson IM, Birnbaum HK. Hydrogen embrittlement of α titanium: *in situ* TEM studies. *Acta Metall* 1988;36:111–24.
- [248] Nelson HG. Hydrogen embrittlement of α titanium: *in situ* TEM studies. *Met Trans* 1973;4:364–7.
- [249] Young GA, Scully JR. Effects of hydrogen on the mechanical properties of a Ti–Mo–Nb–Al alloy. *Scr Met Mater* 1993;28:507–12.
- [250] Kolman DG, Scully JR. Effects of the environment on the initiation of crack growth. West Conshohocken, PA: ASTM; 1997. pp. 61–73
- [251] Costa JE, Williams JC, Thompson AW. *Met Trans* 1987;A23:1421–30.
- [252] Nakamura H, Koiwa M. Hydride precipitation in titanium. *Acta Metall* 1984;32:1799–807.
- [253] Wipf H, Kappesser B, Werner R. Hydrogen diffusion in titanium and zirconium hydrides. *J Alloys Compd* 2000;310:190–5.
- [254] Tsai MM, Howe JM. Lengthening kinetics of (0110) γ -TiH precipitates in α -Ti in the temperature range of 25°C to 80°C. *Met Trans* 1995;A26:2219–26.
- [255] Hua F, Mon K, Pasupathi P, Gordon G, Scoesmith D. Modeling the hydrogen-induced cracking of titanium alloys in nuclear waste repository environments. *J Metals* 2005;57:20–6.
- [256] Murai T, Ishikawa M, Miwa C. The absorption of hydrogen into titanium under cathodic polarization. *Corr Eng* 1977;26:177–83.
- [257] Lane IR, Cavallaro JL, Morton AGS. Sea-water embrittlement of titanium. In: ASTM STP 397, Stress-corrosion cracking of titanium. 1966. pp. 246–58.
- [258] Yokoyama K, Hamada K, Moriyama K, Asaoka K. Degradation and fracture of Ni–Ti superelastic wire in an oral cavity. *Biomaterials* 2001;22:2257–62.
- [259] Yokoyama K, Kaneko K, Moriyama K, Asaoka K, Sakai J, Nagumo M. Delayed fracture of Ni–Ti superelastic alloys in acidic and neutral fluoride solutions. *J Biomed Mater Res* 2004;69A:105–13.
- [260] Yokoyama K, Kaneko K, Moriyama K, Asaoka K, Sakai J, Nagumo M. Hydrogen embrittlement of Ni–Ti superelastic alloy in fluoride solution. *J Biomed Mater Res* 2003;65A:182–7.

This page intentionally left blank

4 Oxidation and Oxides

4.1 Introduction

It is well recognized that the first reaction of a vital hard/soft tissue (i.e., *host tissue*) to any type of biomaterial (ceramics, polymers, metals and alloys, composites) is a rejection; accordingly, biomaterial is normally recognized as a “*foreign material*” by the host tissue. The biological acceptance of these foreign materials by the living tissues is essentially controlled by surface and interfacial reactions between the organic substance and inorganic substrate. The surface is not just a free end of a substance, but it is a contact and boundary zone with other substances (either in gaseous, liquid, or solid). Surface activities may vary from mechanical actions (fatigue crack initiation and propagation and stress intensification), chemical action (discoloration, tarnishing, contamination, corrosion, and oxidation), mechanochemical action (corrosion fatigue and stress-corrosion cracking), thermomechanical action (thermal fatigue), tribological and biotribological actions (wear and wear debris toxicity and friction) to physical and biophysical actions (surface contact and adhesion, wettability, adsorption, absorption, diffusion, and cellular attachment). Accordingly, the longevity, safety, reliability, and structural integrity of dental and medical materials and devices are greatly governed by these surface phenomena, which can be detected, observed, characterized, and analyzed by virtue of various means of devices and technologies [1–3].

To determine and evaluate the biological, mechanical, and morphological compatibilities of biomaterials against receiving human hard/soft tissues, it is also important to understand the interfacial phenomena between the biomaterial and the biological system into/onto which the material is to be implanted [3]. At such an interface, the molecular constituents of the biological system meet and interact with the molecular constituents on the surface of the biomaterials [4]. Since these interactions occur primarily on the molecular level and in a very narrow interface zone having a width of less than 1 nm (1 nanometer = 0.001 μm = 0.1 $\text{\AA}$), surface properties on an atomic scale, and in particular the composition and structure of surface layers of the biomaterial, may play an important role in interfacial phenomena [2]. Hence, surface and interface characterizations and their biochemical and biomechanical roles in biological environments are one of the most important aspect in implantology.

Surfaces and interfaces behave completely different from bulk properties. The characteristics of a biomaterial surface govern the processes involved in biological

response. Surface properties such as surface chemistry, surface energy, and surface morphology may be studied in order to understand the surface region of biomaterials. The surface plays a crucial role in biological interactions for four reasons: (1) the surface of a biomaterials is the only part contacting with the bioenvironment; (2) the surface region of a biomaterial is almost always different in morphology and composition from the bulk; (3) for biomaterials that do not release or leak biologically active or toxic substance, the characteristics of the surface governs the biological response (foreign material versus host tissue); and (4) some surface properties such as topography affect the mechanical stability of the implant–tissue interface [3, p. 313–14, 5–9]. Like the interface, the surface has a certain characteristic thickness: (a) for the case when the interatomic reaction is dominant, such as wetting or adhesion, atoms within a depth of 100 nm (1000 Å) will be important; (b) for the case of the mechanical interaction, such as tribology and surface hardening, since the elasticity due to the surface contact and the plastically deformed layer will be a governing area, the thickness of about 0.1–10 μm will be important; and (c) for the case when mass transfer or corrosion is involved, the effective layer for preventing the diffusion will be within 1–100 μm [5–9].

Such important surfaces can be further modified or altered in a favorable fashion to accommodate, facilitate, or promote more biofunctionality and bioactivity in mechanical, chemical, electrochemical, thermal, or any combination of these methods. When speaking about the surface of titanium materials, it should be always noticed that titanium surface is covered with titanium oxide (titania) with different thicknesses, depending on the previous treatments. This chapter will review and analyze what is known and developed in various areas relevant to titanium oxide—its types and formation, crystalline structures, and applications.

4.2 Formation of Titanium Oxides

Titanium is a highly reactive metal and will react within microseconds to form an oxide layer when exposed to the atmosphere [10]. Although the standard electrode potential was reported in a range from -1.2 to -2.0 V for the $\text{Ti} \leftrightarrow \text{Ti}^{+3}$ electrode reaction [11,12], due to strong chemical affinity to oxygen, it easily produces a compact oxide film, ensuring high corrosion resistance of the metal. This oxide, which is primarily TiO_2 , forms readily because it has one of the highest heats of reaction known ($\Delta H = -915$ kJ/mol) (for 298.16–2000° K) [12, p. D-27, 13,14]. It is also quite impenetrable by oxygen (since the atomic diameter of Ti is 0.29 nm, the primary protecting layer is only about 5–20 atoms thick) [15].

The formed oxide layer adheres strongly to the titanium substrate surface. The average bond strength of the TiO_2 to Ti substrate was reported to be about 300 kcal/mol, while it is 180 kcal/mol for $\text{Cr}_2\text{O}_3/\text{Cr}$, 320 kcal/mol for $\text{Al}_2\text{O}_3/\text{Al}$, and 420 kcal/mol for both $\text{Ta}_2\text{O}_5/\text{Ta}$ and $\text{Nb}_2\text{O}_5/\text{Nb}$, respectively [16]. Adhesion and adhesive strength of Ti oxide to substrates are controlled by oxidation temperature and thickness of the oxide layer as well as the significant influence of nitrogen

on oxidation in air. In addition, adhesion is greater for oxidation in air than in pure oxygen [17], thus suggesting that the influence of nitrogen on the oxidation process is significant.

In addition to these oxidation conditions, it is well known that several parameters can modify the accommodation of the stresses developed during the oxidation of a metal and consequently play an important role in maintaining the protective properties of oxide layers. The results show that (i) the adhesion of the oxide layers to the metal substrate decreases as the layer thickness increases and (ii) it decreases when the oxidation temperature increases, despite the increase in oxide plasticity [16, p. 142–143]. Adhesive strength of TiO_2 to Ti substrate is also related to the thermal mismatching when the Ti/ TiO_2 couple was subjected to the elevated temperatures. Although TiO_2 does not exhibit any phase transformation up to its melting point (i.e., 1885°C), its substrate Ti metal has an allotropic phase transformation at 885°C (below which it is HCP—a hexagonal closed-packed crystalline structure—and above which it becomes BCC—a body-centered cubic crystalline structure). Accordingly, when Ti substrate is exposed beyond this phase transformation temperature, the bond strength between Ti and TiO_2 will be weakened due to the significant differences in coefficients of thermal expansion, particularly during the cooling stage passing through the 885°C transus temperature.

The performance of titanium and its alloys in surgical implant applications can be evaluated with respect to their biocompatibility and capability to withstand the corrosive species involved in fluids within the human body [18], which may be considered as an electrolyte in an electrochemical reaction. It is well documented that the excellent corrosion resistance of titanium materials is due to the formation of a dense, protective, and strongly adhered film—which is called a passive film. Such a surface situation is referred to as passivity (or a passivation state). The exact composition and structure of the passive film covering titanium and its alloys is controversial. This is the case not only for the “natural” air oxide but also for films formed during exposure to various solutions, as well as those formed anodically through an electrochemical reaction. The “natural” oxide film on titanium ranges in thickness from 2 to 7 nm, depending on such parameters as the composition of the metal and surrounding medium, the maximum temperature reached during the working of the metal and the surface finish.

4.2.1 Air-Formed Oxide

When fresh titanium is exposed to the atmosphere by such cutting acts as lathing, milling, or sawing, an oxide layer begins to form within nanoseconds [15]. After only 1 s, a surface oxide will be formed. Air oxidation at room temperature produced titanium monoxide (TiO) with small quantities of titanium oxide, Ti_3O_5 . Titanium has proved to be a highly successful material for implants inserted into human bone. Under certain conditions, titanium will establish and maintain a direct contact with the bone tissue in a process called osseointegration. The mechanisms underlying this behavior are not yet understood. However, it is clear that the properties of the implant surface are of vital importance for a successful osseointegration.

The properties of titanium implant surfaces are determined by the thin (20–70 Å) oxide film that covers the metal. Thus, the biocompatibility of titanium implants is associated with the surface titanium oxide and not with the bulk titanium metal [10,19–21]. The surface oxide is also formed during the implant preparation procedures. During the machining of the implants, pure titanium metal is exposed to air and is rapidly oxidized. In the following cleaning and autoclaving procedures, oxide film is then modified and grows. In order to obtain an oxide film that is reproducible with respect to the chemical composition, structure, and thickness, it is important that the different steps of the implant preparation are performed under carefully controlled conditions. Even small changes in the preparation procedures might lead to considerable changes of the implant surface [22].

As mentioned previously, because the surface air-formed oxide is nearly impenetrable, once this thin passivating film has formed, oxygen is prevented from reaching the metal beneath and further oxide layer thickening is quickly halted because the oxide film is dense and semiconductive (not like an electron-conductive metal substrate). The compositional structure and exact thickness of the passivating oxide layer is dependent on many factors associated with its formation. These include such factors as type of machining, surface roughness, coolants used during machining, and sterilization procedures. It should be no surprise that reported biocompatibility of devices is prepared by different investigators, and therefore may vary to a significant degree [15].

It is well recognized that the excellent tissue–bone compatibility of titanium is mainly due to the properties of its stable surface oxide layer. Biocompatibility of implant materials relies on the chemical and electrochemical stability of this surface oxide layer, which interfaces with the soft and hard tissue and bone structure. Oxide layers formed on titanium change from lower to higher oxides as oxidation progresses and temperature increases. The following phases form in air: $\text{Ti} + \text{O} \rightarrow \text{Ti(O)} \rightarrow \text{Ti}_6\text{O} \rightarrow \text{Ti}_3\text{O} \rightarrow \text{Ti}_2\text{O} \rightarrow \text{TiO} \rightarrow \text{Ti}_2\text{O}_3 \rightarrow \text{Ti}_3\text{O}_5 \rightarrow \text{TiO}_2$. Among these oxides of different stoichiometry (e.g., TiO , Ti_2O_3 , TiO_2), TiO_2 is the most common and stable thermodynamically. TiO_2 can have three different crystal structures (rutile, anatase, and brookite) but also can be amorphous. TiO_2 is very resistant against chemical attack, which makes titanium one of the most corrosion-resistant metals.

Another physical property that is unique to TiO_2 is its high dielectric constant, which ranges from 14 to 110 (in 10^6 cycles; dielectric strength: 350 V/mil, volume resistivity: 10^{14} – 10^{16} Ω cm) depending on crystal structure [12, p. E-58]. This high dielectric constant would result in considerably stronger van der Waal's bonds on TiO_2 than on other oxides. TiO_2 , like many other transition metal oxides, is catalytically active for a number of inorganic and organic chemical reactions, which also may influence the interface chemistry (<http://en.wikipedia.org/wiki/Titanium>).

4.2.2 Passivation

Passivity is a property of a metal commonly defined in two ways. One of these is based on a change in the electrochemical behavior of the metal, and the other on

its corrosion behavior [23]. Passivity is an unusual phenomenon observed during the corrosion of certain metals, indicating a loss of chemical or electrochemical reactivity under certain environmental conditions [24]. Such passivity appears on certain so-called passivating metals, many of which are “transition metals,” characterized by an unfilled d group of electrons in an inner electron shell. Passivating metals are, for example, Fe (covered with Fe_2O_3 and/or Fe_3O_4), Cr (with Cr_2O_3), Zr (with ZrO_2), and Ti (with TiO_2) [25]. This type of passivity is ascribed to an invisibly thin but dense and semiconducting oxide film on the metal substrate surface, displacing the electrode potential of the metal strongly in the positive (or more noble) direction (e.g., Ti passive film exhibits its stable passivity up to 1.5–2.0 V, depending on the chemistry of used electrolyte). Hence, comparing the electrode potential (–1.2– –1.5 V) to this stable passivity potential, surface nobility was remarkably improved.

Passive films can be formed by either chemically or electrochemically (or anodic) treating titanium surfaces. Fraker and Ruff [26] found that more rigid oxidizing conditions produce higher oxides of titanium alloy (thin films) in saline water (3.5% NaCl), at a temperature range between 100°C and 200°C, using a transmission electron microscopy. They found that oxides ranged from Ti_2O to TiO_2 (anatase), with the higher oxides corresponding to the higher temperatures. Concerning oxide films formed anodically on titanium, most investigators agree that the film consists of TiO_2 . All three crystalline forms of TiO_2 (rutile, anatase, and brookite) have been reported, as will be discussed in detail later. In addition to variations in oxygen stoichiometry, the films may contain various amounts of elements other than titanium and oxygen, or incorporate such additional element(s) into TiO_2 structure. Thus, it is most probable that the anodic film is not necessarily stoichiometric TiO_2 and that the films studied by different authors had different compositions due to differences in the conditions of oxidation [26].

When titanium alloys (Ti–6Al–7Nb and Ti–6Al–4V) were chemically treated, surface oxide films appear to be more complicated. Sittig et al. [27] treated these alloys along with CpTi in nitric acid hydrogen fluoride and identified formed oxides. Three types of oxides (TiO_2 , Ti_2O_3 , and TiO) were identified on the CpTi substrate, and it was found that the dissolution rate depends on grain orientations. On the other hand, for Ti–6Al–7Nb and Ti–6Al–4V alloys, Al_2O_3 , Nb_2O_5 , or V-oxides (such as V_2O_5), were formed in addition to TiO_2 oxide, and it was found that the selective α -phase dissolution and enrichment of the β -phase appears to occur [27].

Study on the nature and properties of thin films formed by the electrolytic oxidation on titanium, which, in turn, determines the behavior of the electrode in the open circuit, indicates the duplex nature of these films [28]. It is common practices with implant industries to treat titanium implant surfaces with acid or alkaline media. In both the acid and the alkaline media, the outer layer of the anodic oxide film was found to be more susceptible to dissolution than the inner layer, thereby indicating a more defective structure of the outer layer. The surface reactivity was found to be higher in oxygen- versus nitrogen-saturated solutions. Galvanostatic anodization of titanium has been studied in N_2 -deaerated, 1N solution of NaOH,

Na_2SO_4 , H_2SO_4 , HCl , HClO_4 , HNO_3 , and H_2PO_4 at 25°C at current densities ranging from 4 to $50 \times 10^{-6} \text{ A/cm}^2$. From formation rate values, the following arrangement of passivation was obtained: (from the highest rate to the lowest rate) $\text{NaOH} > \text{Na}_2\text{SO}_4 > \text{HClO}_4 > \text{HNO}_3 > \text{HCl} > \text{H}_3\text{PO}_4 > \text{H}_2\text{SO}_4$ [28].

Metikoš-Huković and Ceraj-Cerić [29] employed structurally sensitive *in situ* methods, such as photopolarization and impedance, to examine the passivation process and the properties of the protective oxide layers on titanium. The thickness of anodic oxidation and the nonstoichiometry of the surface oxide were correlated. It was mentioned that the composition of the anodic film on titanium changes with the relative potential from lower to higher oxidation stages according to the equation: $\text{TiH}_2 + \text{TiO} \rightarrow n\text{Ti}_2\text{O}_3 \cdot n\text{TiO}_2 \rightarrow \text{Ti}_5\text{O}_9$ or $\text{Ti}_6\text{O}_{11} \rightarrow \text{Ti}_3\text{O}_5 \rightarrow \text{TiO}_2$. The characteristic behavior of titanium can easily be seen at higher anodic potential (approximately $+1.5 \text{ V}$ versus SCE in $5 \text{ mol H}_2\text{SO}_4$) when the electrode is covered with a nearly stoichiometric TiO_2 layer. The semiconducting properties of TiO_2 were investigated using an anodic film stabilized at $+2 \text{ V}$ (versus SCE: saturated calomel electrode with 0.24 V versus NHE), and it was found that TiO_2 , like the lower titanium oxides, is an n-type (metal-excess) semiconductor under anodic polarization [29].

Recently, further studies on anodic passivation have been conducted in various electrolytes. For example, it was reported that titanium surfaces were covered by titania layers of anatase and/or rutile by the two-step anodizing in CH_3COOH , followed by H_2SO_4 [30]. Moreover, by passivation treatment in H_2SO_4 and Na_2SO_4 electrolytes, titanium surface was covered by anatase and/or rutile crystal, while amorphous titania films were identified after anodizing in CH_3COOH and H_3PO_4 electrolytes [31]. Yang et al. [32] found that titanium surface was covered by anatase titania by acid treatment at room temperature in $\text{H}_2\text{O}_2/\text{HCl}$ solution, followed by heating in air at 400°C , which confirms what was reported previously by the present author [33].

Repassivation capability [34] associated with titanium substrate can be considered as another reason for the high corrosion resistance and biocompatibility of titanium materials. Although titanium owes its high corrosion resistance to the presence of an extremely thin oxide, when the thin film is disrupted mechanically, underlying metal substrate will react quickly with the surroundings to reform the oxide film. The mechanical and electrochemical parameters associated with the fracture and repassivation of titanium oxide films were studied [35]. Such capability of repassivation is sometimes called a self-healing ability.

4.2.3 Oxidation at Elevated Temperatures

Above 100°C , the surface is a lower oxide type, such as TiO . At elevated temperatures (above 200°C), complex oxides are formed, such as Al_2TiO_5 on $\text{Ti}-6\text{Al}-4\text{V}$ and NiTiO_3 on TiNi , in addition to rutile-type TiO_2 [18,19]. Oxidation in air at $875-1050^\circ\text{C}$ produced a flaky scale of TiO , Ti_2O_3 , and rutile (TiO_2). It was reported that the highest order oxide, TiO_2 , appears on the surface of titanium in the presence of the most rigid conditions of oxidation; in less rigid conditions, a

lower oxide ($3\text{Ti}_2\text{O}_3 \cdot 4\text{TiO}_2$) forms, while in still weaker oxidizing conditions, the formation of even lower oxides (e.g., TiO) are possible [16].

The characteristics of high-temperature oxidation of Ti are the main obstacle to strong Ti—ceramic bonding [36]. A thin oxide layer (about 32 nm) with good adherence to the substrate was formed when CpTi was oxidized at 750°C in 0.1 atm, and a thick layer (ca. $1\ \mu\text{m}$) with poor adherence was formed when oxidized at 1000°C [37]. In another study [38], the thickness of TiO_2 on the CpTi surface increased with an increase in oxidation temperatures. Ti surface hardness also increases substantially after oxidation at/above 900°C [37]. Therefore, the substrate is now in the BCC structure range. Lower Ti—ceramic bond strength was attributed to a thick TiO_2 zone on the metal surface when Ti was oxidized at higher temperatures [39]. Enhanced bond strength between titanium and ceramic was reported when porcelain was fired on cast Ti in a reduced argon atmosphere [40]. Modifying Ti surfaces to control high-temperature oxidation has been examined. Published studies show that Ti surface nitridation [41] or a thin Cr coating [42] is an effective method of limiting Ti oxidation at high temperatures. Improved Ti—ceramic bonding was found when a thin layer of Si_3N_4 was deposited on Ti surface [43].

Recently, microarc oxidation technique [44–46] was employed for surface modification of titanium implants. It was, for example, used to perform titanium coating onto Co—Cr alloy implant surfaces and found that TiO_2 film was identified [44]. An unique method for surface modification onto titanium substrate has been developed by Yamamoto et al. [47]. Titanium surface was previously coated with PVA (polyvinyl alcohol) and thermally treated at 700°C in an ultrapure argon atmosphere, generating a formation of anatase-type TiO_2 with a concentration gradient of oxygen into titanium substrate—oxygen-diffused titanium [47]. It was furthermore reported that the oxygen-diffused titanium possesses *in vitro* apatite formation ability after being soaked into simulated body fluid (SBF) solution and thus incorporated apatite formation ability is attributed to the presence of the anatase titania outermost surface layer and to abundant hydroxyl group formed on the oxygen-diffused titanium surface after SBF immersion [47].

Since oxide film formed on titanium substrate becomes colorful, there are several types of colored titanium accessories on the market. If monochromatic light falls normally on a film-covered metal, some being reflected at the film—air interface and some being refracted by the film and reflected from the metal—oxide interface, interference occurs when the film thickness is proportional to the wavelength of the light. When white light falls on the thin film, interference of certain wavelengths can occur, depending on the film thickness, and the light reaching the eye is colored if the wavelengths subject to interference are within the visible region of the spectrum.

Table 4.1 shows such interference colors when CpTi, Ti—6Al—4V and TiNi coupons are in-air oxidized at various temperatures (resulting in different oxide film thicknesses) at 30 min. The present author has prepared this table to assist in understanding visually the interference colors created on various titanium materials.

Table 4.1 Summary of Interference Colors, After In-Air Oxidation for 30 min

Materials	Temperature				
	350°C	450°C	550°C	650°C	750°C
CpTi (II)	Yellowish blue	Brown	Blue	Light green	Bright gray
Ti–6Al–4V	Yellow	Violet	Greenish blue	Bright gray	Light gray
TiNi	Metallic color	Light yellow	Violet	Blue	Reddish violet

4.3 Influences on Biological Processes

Sundgren et al. [48] and McQueen et al. [49], using Auger Electron Spectroscopy (AES) to study changes in the composition of the titanium surface during implantation in human bone, observed that the oxide formed on titanium implants grows and takes up minerals during the implantation. The growth and uptake occur even though the adsorbed layer of protein is present on the oxide, indicating that mineral ions pass through the adsorbed protein. Liedberg et al. [50], using Fourier Transform InfraRed Reflection Absorption Spectroscopy method, showed that phosphate ions are adsorbed by the titanium surface after the protein has been adsorbed. Using X-ray photoelectron spectroscopy, Hanawa [51] demonstrated that oxides formed on CpTi and Ti–6Al–4V change into complex phosphates of titanium and calcium containing hydroxyl groups which bind water on immersion in artificial saliva (pH 5.2). All these studies [48–51] indicate that the surface oxide on titanium reacts with mineral ions, water, and other constituents of biofluids, and that these reactions, in turn, cause a remodeling of the surface.

It was shown that titanium is in almost direct contact with bone tissue, separated only by an extremely thin cell-free noncalcified tissue layer. Transmission electron microscopy revealed an interfacial hierarchy that consisted of a 20–40 nm thick proteoglycan layer within 4 nm of the titanium oxide, followed by collagen bundles as close as 100 nm and Ca deposits within 5 nm of the surface [52]. To reach the steady-state interface described, both the oxide on titanium and the adjacent tissue undergo various reactions. The physiochemical properties of titanium have been associated with the unique tissue response to the materials: these include the biochemistry of released corrosion products, kinetics of release and the oxide stoichiometry, crystal defect density, thickness, and surface chemistry [53].

While the conditions to produce an optimal oxide formation need to be better understood, in general, the titanium passivating layer not only produces good corrosion resistance but also seems to allow physiological fluids, proteins, and hard and soft tissues to come very close and/or deposit on it directly. Reasons for this are still largely unknown, but it may have something to do with things such as the high dielectric constant for TiO₂ (50–170 versus 4–10 for alumina and dental porcelain) which should result in considerably stronger van der Waal’s bonds on TiO₂ than other oxides; TiO₂ may be catalytically active for a number of organic and inorganic chemical interactions influencing biological processes at the implant

interface (<http://en.wikipedia.org/wiki/Titanium>). The TiO_2 oxide film may permit a compatible layer of biomolecule to attach [54,55].

During implantation, titanium releases corrosion products into the surrounding tissue and fluids even though it is covered by a thermodynamically stable oxide film [56–58]. An increase in oxide thickness, as well as incorporation of elements from the extracellular fluid (P, Ca, and S) into the oxide, has been observed as a function of implantation time [48]. Moreover, changes in the oxide stoichiometry, composition, and thickness have been associated with the release of titanium corrosion products *in vitro* [59]. Properties of the oxide, such as stoichiometry, defect density, crystal structure and orientation, surface defects, and impurities, were suggested as factors determining biological performance [21,26,60].

Titania has been extensively employed as a useful material for anti-UV agents, some cosmetic products, mixing into cold pills as an inactive ingredient, and as a light-activated photocatalyst to decompose contaminants under a reaction with light. However, such fine or ultrafine particles might cause cancer [61]. The results not only of animal experiments but also of many epidemiologic surveys and volunteer intervention experiments in humans reported on the health effects of these particles, including titania powder. The report stated that regardless of dosage and administration method (e.g., inhalation, endotracheal administration, nasal drip, or subcutaneous administration), once nanomaterials enter the bloodstream of a pregnant mother mouse, they move to the offspring and have effects on them; these effects may appear as various symptoms in the process of growth after birth, and can sometimes lead to the onset and aggravation of serious diseases [61].

Olmedo et al. [62] indicated that the titanium oxide (consisted of anatase- and rutile-type titanium dioxides) is prone to breaking, releasing particles to the environment. As a result, corrosion might cause implant failure and body contamination. Based on their previous finding that anatase TiO_2 was deposited in organs with macrophagic activity, transported in the blood by phagocytic mononuclear cells, and induced an increase in the production of reactive oxygen species, they evaluated the effects of rutile TiO_2 . Male Wister rats were injected with a suspension of rutile TiO_2 powder at a dose of 1.60 g/100 g. Six months postinjection, the presence of Ti was assessed in serum, blood cells, liver, spleen, and lungs. Ti was found in phagocytic mononuclear cells, serum, and in the parenchyma of all the organs tested. It was further reported that rutile TiO_2 generated a rise in the percentage of reactive cells, which was smaller than that observed when anatase TiO_2 was employed in their previous study. It was therefore concluded that (i) although rutile TiO_2 provoked an augmentation of reactive oxygen species, it failed to induce damage to membrane lipids due to an adaptive response, and (ii) rutile TiO_2 is less bioreactive than anatase TiO_2 .

4.4 Crystal Structures of Titanium Oxides

It should be clear that the proven high biocompatibility of titanium as an implant materials is connected with the properties of its surface oxide. TiO_2 possesses three

crystalline structures: anatase, rutile, and brookite. Anatase-type TiO_2 is a tetragonal crystalline system with $a_0 = 3.78 \text{ \AA}$ and $c_0 = 9.50 \text{ \AA}$; the rutile-type TiO_2 is also a tetragonal structure, but the lattice constants are quite different from those of anatase type (i.e., $a_0 = 4.58 \text{ \AA}$ and $c_0 = 2.98 \text{ \AA}$). The third type is brookite type and has an orthorhombic crystalline structure with $a_0 = 9.17 \text{ \AA}$, $b_0 = 5.43 \text{ \AA}$, and $c_0 = 5.13 \text{ \AA}$ [63]. Among these oxides, rutile is known to be the most stable phase [64].

Identification of crystalline structures of formed oxides can be achieved by several ways. Thin film X-ray diffraction (TFXRD) or XRD if the oxide film is reasonably thick enough, so that diffracted intensities can be obtained which are high enough to be identified and differentiated from each other and from background noise. The alternative way will be diffraction using accelerated electrons. If an appropriate sample holding device can be manufactured and installed inside the transmission electron microscopy, then the oxidized sample with surface oxide can be tilted almost parallel to the accelerated electron beam, resulting in a half ring of reflection electron diffraction (RED) [65–67], from which one can identify the crystalline structure(s) of the oxide(s). Another method of crystalline identification of formed oxides is based on stripping (or isolating) formed oxide from the substrate by chemically etching the backside (the interface side of formed oxide and substrate) to be isolated from the metallic substrate. Normally for stainless steel, 10% bromine in anhydrous methanol solution is used [67,68], and for titanium materials, a mixed acid of HNO_3 and HF is used [69] or 10% bromine in ethyl acetate [64]. The stripped thin oxide film is carried on a copper mesh and transmission electron diffraction (TED) can be performed [33,69].

For the diffraction method, Bragg's law [70,71] is fully used to calculate the interdistance between diffracted planes, d , in the equation: $n\lambda = 2d \sin \theta$ (where n is the diffraction order and normally equal to one, λ is the wavelength of used diffraction beam, and θ is a diffraction Bragg's angle). For the X-ray diffraction, the wavelength λ is ranged roughly from 1 to 2 $\text{\AA}$ (e.g., $\lambda_{\text{Cu}} = 1.54 \text{ \AA}$, $\lambda_{\text{Mo}} = 0.71 \text{ \AA}$, $\lambda_{\text{Fe}} = 1.94 \text{ \AA}$), so that 2θ reaches its limitation of 180° with $d = 0.5 \text{ \AA}$. On the other hand, for electron diffraction, λ can be approximated by $\lambda = (150/V)^{1/2}$, where V is an accelerated voltage. If $V = 50 \text{ kV}$, $\lambda \approx 0.055 \text{ \AA}$, and if $V = 100 \text{ kV}$, $\lambda \approx 0.038 \text{ \AA}$. Accordingly, with such an accelerated electron, 2θ can be 5×10^{-2} radian $\approx 3^\circ$ for a crystalline structure with $d = 0.5 \text{ \AA}$. Therefore, 2θ is so small that $n\lambda = 2d \sin \theta$ can be simplified as $\lambda = 2d\theta$ (if $n = 1$, as normal). Because θ is small, it can be substituted by r (which is a radius of obtained diffraction ring). Furthermore, if λ is kept constant (which is usually the case), we have $\lambda = 2dr = \text{constant}$. For most studies (e.g., [33,68,69]), a thin fully annealed gold foil (Au) is used as a standard sample, with which $2dr = \text{const.}$ can be further developed to $2d^{\text{Au}} r^{\text{Au}} = \text{constant} = 2d^{\text{sample}} r^{\text{sample}}$. Once all diffracted d-spacings are determined, the crystalline structure can be identified by referring to the XRD Data File [72].

Information on titanium oxides of anatase type, rutile type, brookite type, or a mixture of these, appears to be scattered. It is useful here to review and summarize these data to determine some common findings. The plasma-assisted

chemical vapor deposition process appears to form *anatase*-type oxide [73,74]. By dry oxidation, the oxides are identified as *rutile*-type oxide, oxidized at 300°C for 0.5 h [19,20], 400°C × 0.75 h [75], 500°C × 3 h [76], 750°C [65], and 875–1050°C [17].

On the other hand, crystalline structures of oxides formed through wet oxidation are varied. Only *rutile*-type TiO₂ was identified by boiling in 5 wt% H₂SO₄ or 10 wt% HCl [33], anodizing with 0.5 M H₂SO₄ at 5–10 V [77], boiling in 10% H₂SO₄ [15], boiling in 10% HCl [78], and treating in 0.5–1 M HCl [79]. A *mixture of rutile- and anatase*-type oxide was found when CpTi was treated in HF/HNO₃/H₂O, followed by heating in 5 mol NaOH at 75°C [33], followed by air oxidation at 600°C × 1 h [33], or boiling in 0.1 wt% H₂SO₄ [73]. On the other hand, mainly anatase, with a small fraction of rutile-type mixture, was identified by anodizing in 40% H₂SO₄ at 8 V [27], and boiling in 10% CrO₃ or 65% HNO₃ × 3 h [27]. When CpTi was treated in alkaline or mildly acid solution, formed oxides were identified to be *solely anatase* type. It can be formed by treating CpTi in an electrolyte containing Ca(H₂PO₄)₂, Ca(COCH₃)₂, and Na(EDTA) (pH 14) [73], 1–10% H₂O₂, followed by in-air oxidation at 500°C × 3 h [76], anodizing in HNO₃ solution [78], 0.1 M Na₂CO₃ or 0.01 M HCl [79], anodizing in 0.1 M H₂SO₄ at 12.5 mA/cm² [80], anodizing in 0.1 M H₂SO₄ at 5 V [81], or anodizing in 1 M H₂SO₄ at 155 V [82]. It was also reported that when CpTi was boiled in 0.2 wt% HCl for 24 h, a *mixture of anatase and brookite* was formed [83].

Summarizing the aforementioned information, as seen in Table 4.2, rutile-type oxides are favored when the CpTi surface is exposed to in-air oxidation at elevated temperature. Processes involved in plasma spraying or vapor deposition result in CpTi surfaces covered with *anatase*-type oxide. In wet oxidation (by either simply boiling or electrochemically anodizing), if the electrolyte (or solution) is a strong acid, the rutile-type oxide is favorable, whereas if the treating solution is mild or alkaline, anatase becomes dominant, with a small fraction of rutile type.

Without identifying the crystalline structure of titania films, there are several pre-oxidized commercially available implant systems; for example, TiUnite and Osseotite. Results from clinical data as well as *in vitro* characterization on these preoxidized titanium surface implant indicated that the titanium oxide surface appears to assist the healing response of the bone–implant interface [84–86].

Table 4.2 Summary of Crystalline Structures of Titanium Oxide, Formed in Different Conditions

Condition	Type of Crystalline Structure of Formed Titanium Oxide		
Physical deposition			Anatase
Dry oxidation	Rutile		
Wet oxidation	Rutile	R + A	Anatase
Solution pH	Low pH (acid)	→	High pH (alkaline)

4.5 Characterization of Oxides

Thermally and electrochemically formed oxides on Ti–6Al–4V were investigated by X-ray photoelectron spectroscopy (XPS), scanning AES (Auger electron spectroscopy), and secondary ion mass spectrometry (SIMS), including depth profiling. The oxide layers on the alloy are predominantly TiO₂ but have considerable concentration of the alloying elements included in the oxide. Al, but not V, is observed in the outermost atomic layers of the oxide. Both Al and V are present at relatively high maximum atomic concentration (Al/Ti ~0.17 and V/Ti ~0.07) inside anodic oxides. The V concentration varies laterally over the surface, reflecting the variation of the V concentration in the underlying metal due to its two phases [87].

The *in situ* Raman spectra of electrochemically anodized (in H₂SO₄ and HNO₃) formed oxide (rutile) films on CpTi electrodes were measured. It was found that (i) at the potential of 10 V, the spectra showed clear evidence for the formation of rutile, and (ii) anatase spectra were found after emersion and drying of the oxide film and were also observed when the oxide film was formed in HNO₃ [78]. The chemical compositions of the anodic oxide films formed on CpTi (grade I) during electropolishing (in methanol + *n*-butanol + perchloric acid) and anodic oxidation (in H₂SO₄, H₃PO₄, or acetic acid) were investigated by microanalytical means. It was found that the formed oxide is mainly TiO₂. However, chemical composition can be modified by anion adsorption and/or incorporation when H₂SO₄ or H₃PO₄ electrolytes are used. Modification of the anodic film composition also occurs during sterilization. Increased Ca and H levels are also observed after autoclaving. It was also found that the oxide thickness depends linearly on the anodizing potential in the range 5–80 V [88]. Electrochemical *in situ* ellipsometry with a focused laser beam (microellipsometry) was used to determine properties of oxide layers on single grains of Ti. The data differ from grain to grain and also a strong dependence on the sample rotation around the normal surface occurs due to the anisotropy of the Ti/TiO₂ system [89].

Dolata et al. [90] developed a new technique to evaluate the equivalent circuit elements of a semiconductor–electrolyte interface, based on impedance measurements over a wide frequency range [91]. The EIS tests were carried out over a wide frequency range (from 0.03 Hz to 10 kHz), analyzing the whole spectrum. It was found that the high-frequency response was mainly determined by semiconductor properties of the anatase and rutile layers, whereas the low frequency one reflects particular morphology of the films [90].

For understanding the complex interfacial phenomena between Ti and a biological system, Hanawa [51] prepared CpTi, Ti–6Al–4V, NiTi, 316L stainless steel, Co–30Cr–5Ni, Ni–20Cr, Au–9Cu–6Ag, Ag–20Pd–15Cu–12Au which were polished and immersed in Hank's electrolyte (pH 7.4) at 37°C for 1 h, 1 day, and 30 days. Such sample surfaces were microanalyzed. It was found that (i) calcium phosphate layers are formed on the passive films of Ti and its alloys, stainless steel, Co–Cr, Ni–Cr alloy, in a neutral electrolyte solution, (ii) the calcium phosphate formed on Ti is similar to apatite, and (iii) in all these materials, the formation of

calcium phosphates is related to the biocompatibility of the material, while the passive oxide films are related to the corrosion resistance [51].

4.6 Unique Applications of Titanium Oxide

As an interesting application of TiO_2 (titania), we can find TiO_2 as an oil paint pigment additive (known as titania white). Such white permanent pigment provides good covering power in paints to improve the durability of paints. Titania white pigment is also added to toothpaste to make it whiter and plastics to improve the durability. Paints made with titania are also excellent reflectors of infrared radiation and are therefore used extensively by astronomers and in exterior paints. It is also used in cement, in gemstones, and as a strengthening filler in paper [25]. Since a fine powder of TiO_2 crystals can scatter ultraviolet rays, fine TiO_2 powder is mixed into the ultraviolet prevention cosmetics (sunscreen agents). It is used as an inactive ingredient in over-the-counter cold medicine. TiO_2 powder is also added to cosmetics to brighten and intensify the color of makeup and in piercings and jewelry. Recently, it was found that TiO_2 possesses a photocatalytic function. A photocatalyst is a material which absorbs light to bring it to higher energy level and provides such energy to a reacting substance to make a chemical reaction occur. When the photocatalyst absorbs the light, positive holes are created in the valence electron band to react with electrons. Such positive holes in TiO_2 react with water or dissolved oxygen to generate OH radicals, which decompose toxic substances. The OH radical is a stronger oxidant than chlorine or ozone for sterilization or disinfection purposes (<http://www.highbeam.com/doc/1G1:102604482/Photocatalyst>).

4.7 Oxide Growth, Stability, and Breakdown

The oxide layer forms spontaneously in air, and normally has a thickness of between 2 and 7 nm, as mentioned previously. During machining, the relatively high surface temperature can produce a much thicker oxide layer [92]. There is much evidence suggesting this layer grows steadily *in vivo*. The stoichiometry of the oxide is similar to titanium oxide (TiO_2) at the surface and changes to a mixture of oxides at the metal–oxide interface [10,93]. According to electrical properties of growing oxides, TiO_2 (as well as ZrO_2) belongs to the n-type semiconductors (or donor types), in which metal-excess can be detected due to the fact that metals ions diffuse slowly inside the already-formed oxides, resulting in oxides that grow at the metal–oxide interface; Cr_2O_3 or FeO , meanwhile, shows p-type (acceptor) semiconducting properties, by which oxygen ions diffuse very slowly in formed oxide, with the result that oxide grows at the oxide–air interface [94]. The surface is also known to have at least two types of hydroxyl groups attached to it [53]. TiO_2 is nonconducting, but electrons can tunnel through the layer. Thin oxide layers can

allow the passage of electrons, leading to conformational changes and denaturing of proteins [95].

For implants located in cortical bone, the thickness of the interfacial oxide layer remain unaffected, while it increases by a factor of 3–4 on samples located in bone marrow [48]. In general, when foreign agents, such as implant material surface particles, are exposed to host tissue, circulating neutrophils and/or monocytes are recruited from the intravascular compartment to the location of the exposure [96]. Following recognition, the particles are encapsulated—literally engulfed by the phagocyte—and lysosomal granules, along with the particles, from a complex unit, the phagolysosome. Simultaneously, in the cytoplasmic vacuoles, enzyme releases occurs and, as a result, degrading of several components takes place. Upon recognition, neutrophils and monocytes experience a “respiratory burst” and during the period, almost 20-fold oxygen consumption by the cells is observed [97]. There is convincing evidence that the consequent increase in oxygen secretion by these cells is mainly the result of this initial respiratory activity [98]. In addition, polymorphonuclear cells have been found to secrete superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) upon activation induced by several stimuli, including immunoglobulins and poisoned bacteria, among others [99].

The interactions between solid surfaces and biological systems are relatively unexplored [100]. The combination of electrochemical methods with surface analytical techniques offers an insight into the composition, thickness, and structure of the surface oxide layer. All reports using XPS techniques [54,101–107] confirmed that the oxide layer on top of Ti–6Al–4V was predominantly TiO_2 , which contains a small amount of suboxides TiO and Ti_2O_3 closer to the metal–oxide interface. The presence of Al and V in the oxide layer was also noted. Sodhi et al. [106] reported that Al and V were present throughout the oxide layer; and Al in the passivated layer was greatly enhanced (26 wt%), while V was reduced (1 wt%). Ask et al. [87] observed Al but not V at the outermost surface, and within the oxide, both alloying elements were enriched. Sundararajan et al. [102] observed oxidized Al, but not oxidized V in the layer. On the other hand, Okazaki et al. [103] observed a small amount of oxidized V. Evidently, the presence of V is relatively ambiguous. Moreover, Maeusli et al. [107] did not observe V at the outermost surface of oxide by XPS or AES, although they detected it by SIMS. In all reports, the oxidation state of Al was Al^{3+} (i.e., Al_2O_3), whereas that of V was reported between V^{3+} and V^{5+} (i.e., V_2O_3 and V_2O_5) [101]. Al and V might be present either as Al_2O_3 and V_2O_5 , respectively, or as ions at interstitial or substitutional sites in the TiO_2 matrix [87].

O’Brien et al. [108] passivated nitinol (NiTi) wires and vascular stent components in 10% nitric acid solution and evaluated electrochemical corrosion behaviors. It was reported that (i) potentiodynamic polarization tests demonstrated a significant increase in breakdown potential for passivated samples (600–700 V versus SCE), compared to heat-treated surfaces (250–300 V versus SCE), (ii) surface analysis indicated that the passivation reduces Ni and NiO content in the oxide and increases TiO_2 content, (iii) long-term immersion tests demonstrated that Ni release from the surface of the material decreases with time and the quantity of

Ni released is lower for passivated samples, and (iv) the improved corrosion resistance is maintained after prolonged immersion in 37 V 0.9% NaCl solution [108].

Pure elements of Ti, Nb, V, Al (with 99.9% purity), Ti–6Al–4V and Ti–6Al–6Nb were tested in 37°C aerated simulated physiological Hank's solution at pH of 6.9. It was found that (i) the excellent passivating properties of the anodically formed oxide film on CpTi (grade IV), and high corrosion resistance of the Ti–6Al–6Nb alloy, have been attributed to the stabilizing effect of Nb⁵⁺ cations on the passive film, by annihilation of stoichiometric defects (anion vacancies) caused by the presence of titanium suboxides, (ii) localized corrosion sensitivity of the Ti–6Al–4V alloy has been correlated to the dissolution of vanadium at the surface film–electrolyte interface coupled with generation of cation vacancies and their diffusion through the film as a part of the solid-state diffusion process, and (iii) the presence of a high concentration of chloride ions (0.15 g L⁻¹) in electrolyte further accelerates these processes [109].

Ohtsuka et al. [110] investigated cathodic reduction behavior of the anodic oxide film on Ti using *in situ* ellipsometry combined with electrochemistry. It was reported that (i) in acidic sulfate solution, the anodic oxide film reductively dissolved into the solution as Ti³⁺, resulting in a reduction in thickness without any significant change in the optical properties of the remaining film, while (ii) in neutral phosphate solution, the anodic oxide film absorbs hydrogen in the hydrogen evolution potential region, resulting in a change in the optical properties without thickness reduction [110].

The equilibrium potentials of film formation are given as a function of the activities of the components of the film substance. Its solubility product with respect to the ions in the electrolyte depends on the electrode potential, since the states of oxidation of the metal in the film and in the electrolyte are often different. Heusler [111] discussed three cases for the kinetics of uniform film formation and dissolution: (1) equilibrium of all components across both interfaces, (2) partial equilibrium of one component at the outer film–electrolyte interface, and (3) irreversible ion transfer at the outer interface. It was found that (i) oxide films formed on Fe, Ti, and Al indicate the specific adsorption of anions at passivating oxide films, (ii) the processes during the incubation time of pitting corrosion are shown to correspond to nonuniform dissolution and formation of the passivating film, and (iii) during the incubation time, electrochemical noise due to chloride ions at passive Fe can be measured [111]. Pit generation on Ti with anodic oxide film, which is formed potentiostatistically in 0.5 mol H₂SO₄ solution, has been studied in 1 mol NaBr solution. It was reported that (i) the distribution of pitting potential obeys the normal probability distribution and pitting potential exhibits a maximum around a formation potential of 6.0 V, and (ii) the pit generation process occurs by the parallel birth and death stochastic model and depends on film formation potential, i.e., the film thickness and properties [112].

Sul et al. [113] studied electrochemical dissolution of anodic oxide films on Ti in H₂SO₄ by the use of an optical-electrolytic cell adapted for *in situ* ellipsometric and electrochemical measurements. Films were grown on electropolished Ti surfaces by anodic oxidation in 0.5 mol/dm³ H₂SO₄ for 30 s in the potential range

from 0 to 100 V. Electrochemical dissolution of these films was performed in the potential range between -0.4 and -0.9 V versus SCE. The potential at which electrochemical dissolution is fastest and homogeneous was determined. In addition, it was shown that for potentials more cathodic than -0.8 V, TiH_2 is formed on the electrode surfaces if polarization lasts sufficiently long [113].

The surface properties of anodic oxides formed on CpTi screw implants as well as air-formed natural oxides on turned CpTi implants were investigated. Anodic oxides were prepared in CH_3COOH to the high-forming voltage of dielectric breakdown and spark formation. It was reported that (i) the oxide thicknesses were in the range of about 200–1000 nm and (ii) the crystal structures of the Ti oxide was amorphous, anatase, and a mixture of anatase and rutile [114].

4.8 Reaction with Hydrogen Peroxide

The insertion of an implant is inevitably associated with an inflammatory response due to the surgical trauma. Whether this reaction will subdue or persist may very well be dependent on the material selected, as well as the site of implantation and the loads put on it [115]. It is most probable that the interaction between material and inflammatory cells, either directly or via mediators of cell activation and migration such as complement factors [116], is of key importance for the biocompatibility of an implanted material. Further, experimental studies suggest that oxygen-free radicals generated in large amounts during the respiratory burst by inflammatory cells are important for the tissue damage and persistence of the inflammatory reaction [117]. Further, it has been observed that an oxide-like layer grows on titanium as well as stainless steel implants *in vivo* during the implantation [48,118]. Model experiments have indicated that hydrogen peroxide in buffered saline solution in the millimolar concentration range produces an oxide-like layer on titanium surfaces *in vitro* [119], and at higher H_2O_2 concentrations several oxidation intermediates are distinguished in the Ti– H_2O_2 system. It is well known that hydrogen peroxide is the one of the strongest oxidizing agents and will increase the redox potential of the system. These observations lead one to believe that *in vivo* interaction of H_2O_2 and oxygen with the titanium would be the cause of the oxide growth observed [99]. It is well known that Ti^{4+} ions will not produce hydroxyl radicals from H_2O_2 ; however, in the presence of the superoxide radical (O_2^-), both H_2O_2 and $\text{OH}\cdot$ may be produced through the action of superoxide dismutase and a cyclic Fenton reaction [120–123]. Such superoxide radical (O_2^-) generated during the metabolic activation is (in the body) enzymatically dismuted by hydrogen peroxide through the reaction: $\text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$. Superoxide or hydrogen peroxide alone is not potent enough in degrading adducts and, therefore, several possible mechanisms, starting from the reaction above have been suggested [123]. As a removal mechanism of bacteria inside the body, neutrophil activates such superoxidants of the cells to generate hydrochlorous acid, which possesses the strongest antibacterial agent among various chlorine compounds.

The most interesting is the Fenton type of reaction, $M^{n+} + H_2O_2 \rightarrow M^{(n+1)+} + OH^\cdot + OH^-$, where the potent hydroxyl radical, $OH^\cdot$ is formed. In the presence of O_2^- , the oxidized metal ion, $M^{(n+1)+}$ is reduced again (to M^{n+}), and a cyclic continuous production of $OH^\cdot$ would occur [124].

Hence, hydroxyl radicals formed from hydrogen peroxide during the inflammatory response are potent agents for cellular deterioration. The behavior of implanted material in terms of its ability to sustain or stop free radical formation may be therefore very important. *In vitro* studies of Ti were carried out by measuring the production of free radicals from H_2O_2 at Ti and TiO_2 surfaces by spin trapping techniques. It was found that there is no sustained hydroxyl radical production at a titanium (oxide) surface, due to the quenching of the Fenton reaction through both trapping and oxidation of superoxide radicals in a $TiO \cdot OH$ adduct. Janzén et al. [124] concluded that the degree of surface-induced hydroxyl radical formation from H_2O_2 through the Fenton reaction may be of importance for the behavior of implanted materials.

Tengvall et al. [125] investigated the role of Ti and TiO_2 , as well as other metals, in the inflammatory response through the Fenton reaction. The $TiO \cdot OH$ matrix formed traps the superoxide radical so that no or very small amounts of free hydroxyl radicals are produced. Ellipsometry and spin trapping with spectrophotometry and electron spin resonance were used to study the interaction between Ti and H_2O_2 . Spectrophotometry results indicated that Ti, Zr, Au, and Al are low free OH-radical producers. It was suggested that a hydrated $TiO \cdot OH$ matrix, after the inflammatory reaction, responded to good ion exchange properties, and extracellular components may interact with the $Ti^{4+} - H_2O_2$ compound before matrix formation. The $TiOOH$ matrix is formed when the H_2O_2 coordinated to the $Ti^{4+} - H_2O_2$ complex is decomposed to water and oxygen [125].

It has been reported that (i) Ti implants inserted in the human body for many years have shown high oxidation rates at the areas relatively adjacent to the Ti implant and (ii) the implants have shown a dark pigmentation due to the interaction with H_2O_2 [126]. Gas evolution was observed on the Ti surface in the presence of H_2O_2 in the phosphate-buffered saline (PBS: 8.77NaCl g/L, 3.58 $Na_2HPO_4 \cdot 12H_2O$, 1.36 KH_2PO_4 , pH 7.2–7.4) solution. This is due to the decomposition of H_2O_2 into water and molecular oxygen according to: $2H_2O_2 \rightarrow H_2O + O_2$, which is catalyzed by the presence of TiO_2 on the surface due to the combined effect of the electron-donating and electron-accepting properties of TiO_2 occurring simultaneously [125], and the formation of some Ti-complex, which can lead to a higher electrode potential [127]. Pan et al. [128] performed electrochemical measurements, XPS, and scanning tunneling microscopy analyses to study the effect of hydrogen peroxide on the passivity of CpTi (grade II) in a PBS solution. The results indicate that the passive film formed in the PBS solution—with and without addition of H_2O_2 —may be described with a two-layer structure model. The inner layer has a structure close to TiO_2 , whereas the outer layer consists of hydroxylated compounds. The introduction of H_2O_2 in the PBS solution broadens the hydroxylate-rich region, probably due to the formation of a $Ti^{4+} - H_2O_2$ complex. Furthermore, the presence of H_2O_2 results in enhanced

dissolution of Ti and a rougher surface on a microscopic scale. It was also observed that H_2O_2 addition furthermore seems to facilitate the incorporation of phosphate ions into the thicker porous layer [128]. The influence of H_2O_2 generated by an inflammatory response has also been suggested as an explanation for the high rate of Ti oxidation/corrosion *in vivo* [117,125,129]. The incorporation of mineral ions into the oxide film is believed to be important for the osseointegration behavior, which can lead to direct bone–titanium contact and strong bonding that, in turn, can contribute to the load-bearing capacity of titanium implants [130].

To analyze titanium's response to representative surgical wound environments, Bearinger et al. [131] examined CpTi and Ti–6Al–4V, which were exposed to the PBS solution with 30 mM with hydrogen peroxide addition. The study was characterized by simultaneous electrochemical atomic force microscopy and step-polarization impedance spectroscopy. It was found that (i) surfaces were covered with protective oxide domes that indicated topography changes with potential and time of immersion and (ii) less oxide dome coarsening was noted on surfaces treated with PBS containing H_2O_2 than on surfaces exposed to pure PBS. In both types of solutions, oxide (early) resistances of CpTi samples were higher than Ti–6Al–4V oxide resistances, but CpTi oxide resistance was lower in the hydrogen peroxide solution compared to pure PBS. Differences in electrical properties between CpTi and Ti–6Al–4V surfaces suggest that CpTi, but not Ti–6Al–4V, has catalytic activity on H_2O_2 , and that the catalytic activity of CpTi oxide affects its ability to grow TiO_2 [131].

4.9 Applications of Advanced Technologies

As the present author has stated [3, p. 406–11, 132,133], implant design concept has to rely on transdisciplinary approach of biomaterials, biological materials, biomimetic materials, their science and engineering; implant manufacturing should employ various advanced technologies and engineering including high-tech spin-off technologies. Since the first edition of this book, nanoscience and nanotechnology have been remarkably advanced.

4.9.1 Nanotube Fabrication

There is a strong belief that nanoscale materials will produce a new generation of implant material with high efficiency, low cost, and high volume. The nanoscale in materials processing is truly a new frontier. Metallic dental implants have been used successfully for decades, but they have serious shortcomings related to their osseointegration and the fact that their mechanical properties do not match those of bone [134]. Oshida [3, p. 143–148] has described this point and has called it mechanical compatibility between implant materials and receiving vital hard tissue. Due to about one decade difference in values of modulus of elasticity between titanium materials and bone, accordingly there could be a large level of interfacial

stress ($\Delta\sigma = \sigma_I - \sigma_B = E_I\varepsilon_I - E_B\varepsilon_B$) at the interface between implant (I) and bone (B), since (i) $E_I > E_B$ and (ii) due to continuous strain environment, $\varepsilon_I = \varepsilon_B$. If such interfacial stress is larger than the bonding strength of bone fused to titanium implant surface, it is obvious that the implant could be detached, leading to implant failure. This mechanical compatibility is important not only for the case between placed implant and hard tissue but also for the case for connecting implant supported tooth and natural tooth. As a result, and for the sake of successful mechanical compatibility, the surface zone should be fabricated or structured to exhibit a low value of modulus of elasticity; accordingly, porous structure and/or nanoscale structure become very practical and effective choices.

Implant failure has been attributed to loosening of an implant from the host bone possibly due to poor osseointegration [135]. It is also mentioned that the native TiO_2 layer is not bioactive enough to form a direct bond with bone, which sometimes translates into a lack of osseointegration into juxtaposed bone that might lead to long-term implant failure [135]. One promising strategy for improving osseointegration is to develop a functional implant surface that promotes osteoblast differentiation [135,136]. The principle technique to produce nanotubes on titanium surface is an anodizing method in electrochemical reaction in electrolyte [135–142], including a mixed acid of 1 M H_3PO_4 and 0.4 wt% HF solution, or 1 M $(\text{NH}_4)_2\text{SO}_4 + 0.25$ M NH_4F . Generally speaking, nanotubes are approximately 100 nm in diameter and 500 nm in length and the porosity is varied from 45% to 65%, depending on the anodizing time and voltage. If the electrolyte contains F ion, it was found that the fluorinated chemistry of the nanotubes of F- TiO_2 , TiOF_2 , and F-TiO with F ion incorporation was approximately 5 at.%. [139,141].

It appears to be that the TiO_2 nanotubes possess potential applications in the field of bone implants and bone tissue engineering [139]. And since TiO_2 nanotube layers/Ti biocomposites had very good antibacterial activity to resist *Streptococcus mutans*, as a dental implant biomaterial, *in situ* TiO_2 nanotube layer/Ti biocomposite has better and wider application prospects [140].

Constructing such TiO_2 nanotubes on different material (Ti–28Zr–8Nb alloy) has been successfully conducted using an electrolyte of a mixture of $(\text{NH}_4)_2\text{SO}_4$ containing NH_4F [141]. It was reported that the results are highly promising for the new biomedical alloy (Ti–Zr–Nb system), as the large surface area and the tunable nanoscale geometry of the surface oxide provide novel pathways for the interaction of the materials with biorelevant species, such as cells and proteins [141]. Furthermore, Xin et al. [142] has developed strontium-releasing implants which are capable of stimulating bone formation and inhibiting bone resorption as a desirable solution for curing osteoporosis. The well-ordered SrTiO_3 nanotube arrays capable of Sr release at a slow rate and for a long time have been successfully fabricated on titanium by simple hydrothermal treatment of anodized titania nanotubes.

4.9.2 Hybrid Oxides Formation

There is a great demand for dental implant surfaces to accelerate the process of periimplant bone generation to reduce its healing time and enable early loading.

Incorporating different particles with titania might help to reduce the value of modulus of elasticity for better situation of mechanical compatibility. To this end, several new materials have been developed, including micro–nano hybridization [143], mixing with peek (poly ether-ether ketone) [144], with silicon [145] and magnesium [146].

4.9.3 Nano Titania Film Formation

In order to alter the surface properties, there have been many modifications developed, and such techniques are conducted chemically, electrochemically, thermally, physically, or combinations of these [147]. Among these surface modification technologies, thin film coating/forming has been extensively advanced to enrich surface layer with certain element(s), to increase hardness for tribological resistance and corrosion resistance, and to promote biological action such as osseointegration.

Thin film of TiO_2 was deposited onto nanoporous alumina templates to expect a significant role in the controlled release of pharmacologic agents for the treatment of cancer [148]. Hu et al. [149] employed a plasma electrolytic oxidation technique to coat zinc-incorporated TiO_2 film onto titanium substrate, claiming that such coatings showed excellent antibacterial activity and biocompatibility as a promising candidate for orthopedic and dental implants. In colloidal chemistry, sol–gel species are successfully adopted with assists from various surrounding technologies to produce nano TiO_2 films; for example, sol–gel and anodic oxidation technique [150,151], sol–gel and spin coating process [152], sol–gel and laser-induced technique [153], and colloidal sol and solvothermal method [154]. Via alternative ways, thin film TiO_2 can be deposited by electrobeam evaporation [155] or chemical vapor deposition [156].

4.9.4 UV Treatment

Titanium dioxide, a photocatalyst, is known to decompose various organic compounds under ultraviolet (UV) illumination by generating various radicals, which is useful for killing bacteria. There are several studies conducted to evaluate the efficacy and efficiency of UV light treatment on the enhancement of osseointegration [157–159]. Although the photoinduced bacterial efficacy of titanium dioxide films is dependent on their surface characteristics and the osseointegration capability evaluation needs more and different animal models, the common finding indicates that (i) complement activating Ti implants elicited a stronger inflammatory response than ozone ultraviolet–treated Ti and (ii) UV light pretreatment substantially enhanced the osseointegration capacity of acid-etched titanium implants.

It has been discussed that it is essential to understand the nature and structure of oxides formed on surfaces of titanium materials because such oxides can control subsequent physical, chemical, and biological behaviors after the implant is placed into/onto vital tissue. Because of such important nature, we have seen that titania (titanium oxide) itself serves as a material for nanotube formation and thin film formation. These forms, along with the foamed structure of titanium solid structures,

should help to reduce the original rigidity of solid metallic titanium bodies, resulting in a more favorable situation for biomechanical compatibility between placed implant and the receiving hard tissue, and, in more challenging cases, for connections between the implant tooth and natural tooth. For future prospects, the scaffold structure and concept which have been extensively employed in tissue engineering can be further utilized in dental and medical implant systems. As a high-tech spin-off technology, the stock-removal process has been successfully adopted for fabricating titanium bone [160], which could alter the conventional design concept for dental and orthopedic implants.

References

- [1] Allen P. Titanium alloy development. *Adv Mater Process* 1996;154:35–7.
- [2] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones—Toward a morphological compatibility of implants. *J Bio-Med Mater Eng* 1994;4:397–407.
- [3] Oshida Y. *Bioscience and bioengineering of titanium materials*. 1st ed Oxford: Elsevier; 2007. pp. 6–8
- [4] Kasemo B, Lausmaa J. Surface science aspects on inorganic biomaterials. *CRC Crit Rev Biocompatibility* 1986;2:335–80.
- [5] Kasemo B, Lausmaa J. Biomaterials and implant surfaces: a surface science approach. *Int J Oral Maxillofac Implants* 1988;3:247–59.
- [6] Baier RE, Meyer AE. Implant surface preparation. *Int J Oral Maxillofac Implants* 1988;3:9–20.
- [7] Reitz WE. The eighth international conference on surface modification technology. *J Met* 1995;47:14–6.
- [8] Smith DC, Pilliar RM, Chernenky R. Dental implant materials. I. Some effects of preparative procedures on surface topography. *J Biomed Mater Res* 1991;25:1045–68.
- [9] Buddy D, Ratner B, Thomas JL. Biomaterial surfaces. *J Biomed Mater Res* 1987;21:59–89.
- [10] Kasemo B. Biocompatibility of titanium implants: surface science aspects. *J Pros Dent* 1983;49:832–7.
- [11] Tomashov ND. *Theory of corrosion and protection of metals: the science of corrosion*. New York, NY: The MacMillan Co.; 1966. p.144
- [12] *CRC handbook of chemistry and physics*. 47th ed. Cleveland: The Chemical Rubber Co.; 1966. p. D-54.
- [13] Ashby MF, Jones DRH. *Engineering materials. An introduction to their properties and applications*. New York, NY: Pergamon Press; 1980. pp. 194–200
- [14] West JM. *Basic corrosion and oxidation*. 2nd ed. London: John Wiley & Sons; 1986. pp. 27–30
- [15] Lautenschlager EP, Monaghan P. Titanium and titanium alloys as dental materials. *Int Dent J* 1993;43:245–53.
- [16] *Oxidation of metals and alloys*. Ohio: American Society for Metals; 1971. p. 46.
- [17] Coddet C, Chaze AM, Beranger G. Measurements of the adhesion of thermal oxide films: application to the oxidation of titanium. *J Mater Sci* 1987;22:2969–74.

- [18] Solar RJ. Corrosion resistance of titanium surgical implant alloys: a review ASTM STP 684 In: Syrett BD, editor. Corrosion and degradation of implant materials. Philadelphia, PA: American Society for Testing and Materials; 1979. p. 259–73
- [19] Oshida Y, Sachdeva R, Miyazaki S. Changes in contact angles as a function of time on some pre-oxidized biomaterials. *J Mater Sci Mater Med* 1992;3:306–12.
- [20] Oshida Y, Sachdeva R, Miyazaki S, Daly J. Effects of shot peening on surfaces contact angles of biomaterials. *J Mater Sci Mater Med* 1993;4:443–7.
- [21] Albrektsson T, Brånemark PI, Hansson HA, Kasemo B, Larsson K, Lundstroem I, et al. The interface zone of inorganic implants *in vivo*: titanium implants in bone. *Ann Biomed Eng* 1983;11:1–27.
- [22] Lausmaa J, Kasemo B, Hansson S. Accelerated oxide growth on titanium implants during autoclaving caused by fluorine contamination. *Biomaterials* 1985;6:23–7.
- [23] Uhlig HH. The corrosion handbook. New York, NY: John Wiley & Sons; 1966. p. 20
- [24] Fontana MG, Greene ND. Corrosion engineering. New York, NY: McGraw-Hill Book; 1967. pp. 319–21
- [25] Wranglén G. An introduction to corrosion and protection of metals. London: Chapman & Hall; 1985. pp. 65–6
- [26] Fraker AC, Ruff AW. Corrosion of titanium alloys in physiological solutions. *Titanium science and technology*, vol. 4. New York, NY: Plenum Press; 1973. pp. 2447–57
- [27] Sittig C, Textor M, Spencer ND, Wieland M, Vallotton P-H. Surface characterization of implant materials cp Ti, Ti–6Al–7Nb and Ti–6Al–4V with different pretreatments. *J Mater Sci Mater Med* 1999;10:35–46.
- [28] Mazhar AA, Heakal FEL-T, Gad-Allah AG. Anodic behavior of titanium in aqueous media. *Corrosion* 1988;44:705–10.
- [29] Metikoš-Huković M, Ceraj-Cerić M. Anodic oxidation of titanium: mechanism of non-stoichiometric oxide formation. *Surf Technol* 1985;24:273–83.
- [30] Xie L, Liao X, Yin G, Huang Z, Yan D, Yao Y, et al. Preparation, characterization, *in vitro* bioactivity, and osteoblast adhesion of multi-level porous titania layer on titanium by two-stereo anodization treatment. *J Biomed Mater Res* 2011;98:312–20.
- [31] Cui X, Kim H-M, Kawashita M, Wang L, Xiong L, Kokubo T, et al. Preparation of bioactive titania films on titanium metal via anodic oxidation. *Dent Mat* 2009;25:80–6.
- [32] Yang X-F, Chen Y, Yang F, He F-M, Zhao S-F. Enhanced initial adhesion of osteoblast-like cells on an anatase-structured titania surface formed by H₂O₂/HCl solution and heat treatment. *Dent Mat* 2009;25:473–80.
- [33] Lim YJ, Oshida Y, Andres CJ, Barco MT. Surface characterization of variously treated titanium materials. *Int J Oral Maxillofac Implants* 2002;16:333–42.
- [34] Hanawa T, Asami K, Asaoka K. Repassivation of titanium and surface oxide film regenerated in stimulated bioliquid. *J Biomed Mater Res* 1998;40:530–8.
- [35] Gilbert JL, Buckley CA, Lautenschlager EP. Electrochemical reaction to mechanical disruption of titanium oxide films. *J Dent Res* 1995;74(Special Issue):92 (Ab. No. 645)
- [36] Hruska AR, Borelli P. Quality criteria for pure titanium casting, laboratory soldering, intraoral welding, and a device to aid in making uncontaminated castings. *J Prosthet Dent* 1999;66:561–5.
- [37] Adachi M, Mackert Jr JR, Parry EE, Fairhurst CW. Oxide adherence and porcelain bonding to titanium and Ti–6Al–4V alloy. *J Dent Res* 1990;69:1230–5.
- [38] Kimura H, Hornig CJ, Okazaki M, Takahashi J. Oxidation effects on porcelain–titanium interface reactions and bond strength. *Dent Mater J* 1990;9:91–9.

- [39] Hautaniemi JA, Herø H. Porcelain bonding on Ti: its dependence on surface roughness, firing and vacuum level. *Surf Interface Anal* 1993;20:421–36.
- [40] Atsü S, Berksun B. Bond strength of three porcelain to two forms of titanium using two firing atmospheres. *J Prosthet Dent* 2000;84:567–74.
- [41] Oshida Y, Hashem A. Titanium–porcelain system. Part I: Oxidation kinetics of nitrided pure titanium, simulated to porcelain firing process. *J Biomed Mater Eng* 1993;3:185–98.
- [42] Wang RR, Fung KK. Oxidation behavior of surface-modified titanium for titanium–ceramic restorations. *J Prosthet Dent* 1997;77:423–34.
- [43] Wang RR, Welsch G, Monteiro O. Silicon nitride coating on titanium to enable titanium–ceramic bonding. *J Biomed Mater Res* 1999;46:262–70.
- [44] Han CM, Kim HE, Kim YS, Han SK. Enhanced biocompatibility of Co–Cr implant material by Ti coating and micro-arc oxidation. *J Biomed Mater Res B Appl Biomater* 2009;90:165–70.
- [45] Li Y, Lee IS, Cui FZ, Choi SH. The biocompatibility of nanostructured calcium phosphate coated on micro-arc oxidized titanium. *Biomaterials* 2008;29:2025–32.
- [46] Guo Z, Zhou L, Rong M, Zhu A, Geng H. Bone response to a pure titanium implant surface modified by laser etching and microarc oxidation. *Int J Oral Maxillofac Implants* 2009;24:130–6.
- [47] Yamamoto O, Alvarez K, Kikuchi T, Fukuda M. Fabrication and characterization of oxygen-diffused titanium for biological applications. *Acta Biomater* 2009;5:3605–15.
- [48] Sundgren J-E, Bodö P, Lundström I. Auger electron spectroscopic studies of the interface between human tissue and implants of titanium and stainless steel. *J Colloid Interface Sci* 1986;110:9–20.
- [49] McQueen D, Sundgren JE, Ivarsson B, Lundstrom I, Af Ekenstam CB, Svensson A, et al. Auger electron spectroscopic studies of titanium implants. In: Lee AJC, editor. *Clinical applications of biomaterials*. New York, NY: Wiley; 1982. p. 179–85.
- [50] Liedberg B, Ivarsson B, Lundstrom I. Fourier transform infrared reflection absorption spectroscopy (FTIR-RAS) of fibrinogen adsorbed on metal and metal oxide surfaces. *J Biochem Biophys Method* 1984;9:233–43.
- [51] Hanawa T. Titanium and its oxide film: a substrate for formation of apatite. In: Davies JE, editor. *The bone–biomaterial interface*. Toronto, ON: University of Toronto Press; 1991. p. 49–61.
- [52] Healy KE, Ducheyne P. Hydration and preferential molecular adsorption on titanium *in vitro*. *Biomaterials* 1992;13:553–61.
- [53] Healy KE, Ducheyne P. The mechanisms of passive dissolution of titanium in a model physiological environment. *J Biomed Mater Res* 1992;26:319–38.
- [54] Brånemark PI. Introduction to osseointegration. In: Brånemark PI, editor. *Tissue-integrated prostheses*. Chicago, IL: Quintessence Publishing; 1985. p. 63–70.
- [55] Kasemo B, Lausmaa J. Metal selection and surface characteristics. In: Brånemark OI, editor. *Tissue-integrated prostheses*. Chicago, IL: Quintessence Publishing; 1985. p. 108–15.
- [56] Meachim G, Williams DF. Changes in nonosseous tissue adjacent to titanium implants. *J Biomed Mater Res* 1973;7:555–72.
- [57] Ferguson AB, Akahoshi Y, Laing PG, Hodge ES. Characteristics of trace ions released from embedded metal implants in the rabbit. *J Bone Joint Surg* 1962;44-A:323–36.
- [58] Ducheyne P, Williams G, Martens M, Helsen J. *In vivo* metal-ion release from porous titanium–silver material. *J Biomed Mater Res* 1984;18:293–308.

- [59] Ducheyne P, Healy KE. Surface spectroscopy of calcium phosphate ceramic and titanium implant materials. In: Ratner BD, editor. Surface characterization of biomaterials. Amsterdam: Elsevier Science; 1988. p. 175–92.
- [60] Albreksson T, Hansson HA. An ultrastructural characterization of the interface between bone and sputtered titanium or stainless steel surfaces. *Biomaterials* 1986;7:201–5.
- [61] Takeda K, Shinkai Y, Suzuki K, Yanagita S, Umezawa M, Yokota S, et al. Health effects of nanomaterials on next generation. *Pharmac Soc Jpn* 2011;131:229–36.
- [62] Olmedo DG, Tasat DR, Evelson P, Guglielmotti MB, Cabrini RL. Biological response of tissues with macrophagic activity to titanium dioxide. *J Biomed Mater Res A* 2008;84(4):1087–93.
- [63] Wyckoff RWG. The structure of crystals. New York, NY: Chemical Catalog Co.; 1931. p. 134, p. 239
- [64] Tang H, Prasad K, Sanjinès R, Schmid PE, Lévy F. Electrical and optical properties of TiO₂ anatase thin films. *J Appl Phys* 1994;75:2042–7.
- [65] Douglass DL, van Landuyt J. The structure and morphology of oxide films during the initial stages of titanium oxidation. *Acta Met* 1966;14:491–503.
- [66] Nakayama T, Oshida Y. Effects of surface working on the structure of oxide films by wet oxidation in austenitic stainless steels. *Trans Jpn Inst Metals* 1971;12:214–7.
- [67] Mahla EM, Nielsen NA. A study of films isolated from passive stainless steels. *Trans Electrochem Soc* 1948;81:913–6.
- [68] Nakayama T, Oshida Y. Identification of the initial oxide films on 18-8 stainless steel in high temperature water. *Corrosion* 1968;24:336–7.
- [69] Kuphasuk C, Oshida Y, Andres CJ, Hovijitra ST, Barco MT, Brown DT. Electrochemical corrosion of titanium and titanium-based alloys. *J Prosthet Dent* 2001;85:195–202.
- [70] Cullity BD. Elements of X-ray diffraction. Reading, MA: Addison-Wesley; 1978. pp. 86–9
- [71] Schwartz LH, Cohen JB. Diffraction from materials. Heidelberg: Springer-Verlag; 1987. pp. 46–9
- [72] X-ray powder data file. Philadelphia, PA: American Society for Testing and Materials; 1960.
- [73] Głuszek J, Masalski J, Furman P, Nitsch K. Structural and electrochemical examinations of PACVD TiO₂ films in Ringer solution. *Biomaterials* 1997;18:789–94.
- [74] Liu X, Ding C. Plasma sprayed wollastonite/TiO₂ composite coatings on titanium alloys. *Biomaterials* 2002;23:4065–77.
- [75] Browne M, Gregson PJ. Surface modification of titanium alloy implants. *Biomaterials* 1994;15:894–8.
- [76] Takemoto S, Yamamoto T, Tsuru K, Hayakawa S, Osaka A, Takashima S. Platelet adhesion on titanium oxide gels: effect of surface oxidation. *Biomaterials* 2004;25:3845–92.
- [77] Allen KW, Alsalam HS. Titanium and alloy surfaces for adhesive bonding. *J Adhes* 1974;6:229–37.
- [78] Felske A, Plieth WJ. Raman spectroscopy of titanium dioxide layers. *Electrochim Acta* 1989;34:75–7.
- [79] Matthews A. The crystallization of anatase and rutile from amorphous titanium dioxide under hydrothermal conditions. *Am Miner* 1976;61:419–24.
- [80] Yahalom J, Zahavi J. Electrolytic breakdown crystallization of anodic oxide films on Al, Ta and Ti. *Electrochimica Acta* 1970;15:1429–35.
- [81] Ohtsuka T. Structure of anodic oxide films on titanium. *Surface Sci* 1998;12:799–804.

- [82] Liang B, Fujibayashi S, Neo M, Tamura J, Kim H-M, Uchida M, et al. Histological and mechanical investigation of the bone-bonding ability of anodically oxidized titanium in rabbits. *Biomaterials* 2003;24:4959–66.
- [83] Koizumi T, Nakayama T. Structure of oxide films formed on Ti in boiling dilute H_2SO_4 and HCl. *Corr Sci* 1968;8:195–9.
- [84] Balshi SF, Wolfinger GJ, Balshi TJ. Analysis of 164 titanium oxide-surface implants in completely edentulous arches for fixed prosthesis. *Int J Oral Maxillofac Implants* 2005;20:946–52.
- [85] Sul Y-T, Byon E, Wennerberg A. Surface characteristics of electrochemically oxidized implants and acid-etched implants: surface chemistry, morphology, pore configurations, oxide thickness, crystal structure, and roughness. *Int J Oral Maxillofac Implants* 2008;23:631–40.
- [86] Bahat O. Technique for placement of oxidized titanium implants in compromised maxillary bone: prospective study of 290 implants in 126 consecutive patients followed for a minimum of 3 years after loading. *Int J Oral Maxillofac Implants* 2009;24:325–34.
- [87] Ask M, Lausmaa J, Kasemo B. Preparation and surface spectroscopic characterization of oxide films on Ti6Al4V. *Appl Surf Sci* 1988/89;35:283–301.
- [88] Lausmaa J, Kasemo B, Mattsson H, Odelius H. Multiple-technique surface characterization of oxide films on electropolished and anodically oxidized titanium. *Appl Surf Sci* 1990;45:189–200.
- [89] Michaelis A, Schultze JW. Effect of anisotropy on microellipsometry in the Ti/TiO₂ system. *Thin Solid Films* 1993;233:86–90.
- [90] Dolata M, Kedzierzawski P, Augustynski J. Comparative impedance spectroscopy study of rutile and anatase TiO₂ film electrodes. *Electrochim Acta* 1996;41:1287–93.
- [91] Tomkiewicz M. Relaxation spectrum analysis of semiconductor–electrolyte interface-TiO₂. *J Electrochem Soc* 1979;126:2220–5.
- [92] Sutherland DS, Forshaw PD, Allen GC, Brown IT, Williams KR. Surface analysis of titanium implants. *Biomaterials* 1993;14:893–9.
- [93] Lausmaa GJ, Kasemo B. Surface spectroscopic characterization of titanium implant materials. *Appl Surf Sci* 1990;44:133–46.
- [94] Kubaschewski O, Hopkins BE. *Oxidation of metals and alloys*. London: Butterworths; 1962. pp. 15–29.
- [95] Tummeler H, Thull R. Model of the metal/tissue connection of implants made of titanium or tantalum. *Biological and biochemical performance of biomaterials*. the Netherlands: Elsevier; 1986. pp. 403–8.
- [96] Eliades T. Passive film growth on titanium alloys: physiochemical and biologic considerations. *Int J Oral Maxillofac Implants* 1997;12:621–7.
- [97] Drath DB, Karnovsky ML. Superoxide production by phagocytic leukocytes. *J Exp Med* 1975;144:257–61.
- [98] Root BK, Metcalf JA. H_2O_2 release from human granulocytes during phagocytosis: relationship to superoxide anion formation and cellular catabolism of H_2O_2 . Studies with normal and cytochalasin β -treated cells. *J Clin Invest* 1977;60:1266–79.
- [99] DeChatelet LR. Oxide bactericidal mechanisms of PMN. *J Infect Dis* 1975;131:295–303.
- [100] Milošev I, Metikoš-Huković M, Strehblow H-H. Passive film on orthopaedic TiAlV alloy formed in physiological solution investigated by X-ray photoelectron spectroscopy. *Biomaterials* 2000;21:2103–13.

- [101] Kovacs P. Electrochemical techniques for studying the corrosion behaviour of metallic implant materials. *Corrosion '92*, NACE Conf Proc 1992;214:1–214.
- [102] Sundararajan T, Kamachi Mudali U, Mair KGM, Rajeswari S, Subbiyan M. Surface characterization of electrochemically for passive film on nitrogen implanted Ti6Al4V alloy. *Mater Trans JIM* 1998;39:756–61.
- [103] Okazaki Y, Tateishi T, Ito Y. Corrosion resistance of implant alloys in pseudo physiological solution and role of alloying elements in passive films. *Mater Trans JIM* 1997;38:78–84.
- [104] Hernandez de Gatica NL, Jones GL, Gardella Jr JA. Surface characterization of titanium alloys sterilized for biomedical applications. *Appl Surf Sci* 1993;68:107–21.
- [105] Pham MT, Zyganow I, Matz W. Corrosion behaviour and microstructure of titanium implanted with α and β stabilizing elements. *Thin Solid Films* 1997;310:251–9.
- [106] Sodhi RNS, Weninger A, Davis JE, Sreenivas K. X-ray photoelectron spectroscopic comparison of sputtered Ti, Ti6Al4V, and passivated bulk metals for use in cell culture techniques. *J Vac Sci Technol A* 1991;A9:1329–33.
- [107] Maeusli P-A, Bloch PR, Geret V, Steinmann SG. In: Christel P, Meunier A, editors. *Biological and biomechanical performance of biomaterials*. Amsterdam: Elsevier; 1986. p. 57.
- [108] O'Brien B, Carroll WM, Kelly MJ. Passivation of nitinol wire for vascular implants—a demonstration of the benefits. *Biomaterials* 2002;23:1739–48.
- [109] Metikoš-Huković M, Kwokal A, Piljac J. The influence of niobium and vanadium on passivity of titanium-based implants in physiological solution. *Biomaterials* 2003;24:3765–75.
- [110] Ohtsuka T, Masuda M, Sato N. Cathodic reduction of anodic oxide films formed on titanium. *J Electrochem Soc* 1987;134:2406–10.
- [111] Heusler KE. The influence of electrolyte composition on the formation and dissolution of passivating films. *Corr Sci* 1989;29:131–47.
- [112] Arsov LJD. Dissolution electrochimique des films anodiques du titane dans l'acide sulfurique. *Electrochim Acta* 1985;12:1645–57.
- [113] Sul Y-T, Johansson CB, Petronis S, Krozer A, Jeong Y, Wennerberg A, et al. Characteristics of the surface oxides on turned and electrochemically oxidized pure titanium implants up to dielectric breakdown: the oxide thickness, micropore configuration, surface roughness, crystal structure and chemical composition. *Biomaterials* 2002;23:491–501.
- [114] Shibata T, Zhu Y-C. The effect of film formation potential on the stochastic processes of pit generation on anodized titanium. *Corr Sci* 1994;36:153–63.
- [115] Tengvall P, Elwing H, Sjöqvist L, Lundström I. Interaction between hydrogen peroxide and titanium: a possible role in the biocompatibility of titanium. *Biomaterials* 1989;10:118–20.
- [116] Jacob HS, Craddock PR, Hammerschmidt DE, Moldow CF. Induced granulocyte aggregation—unsuspected mechanism of disease. *N Engl J Med* 1980;302:789–94.
- [117] Del Masestro RF. An approach to free radicals in medicine and biology. *Acta Physiol Scand* 1980;492(Suppl):153–68.
- [118] Sundgren J-E, Bodö P, Lundström I, Berggren A, Hellem S. Auger electron spectroscopic studies of stainless steel implants. *J Biomed Mater Res* 1985;19:663–71.
- [119] Tengvall P, Bjursten LM, Elwing H, Lunström I. Free radicals oxidation of metal implants and biocompatibility. 2nd International Conference Biointeractions '87. London; 1987.

- [120] Jaeger CD, Bard AJ. Spin-trapping and electron spin resonance detection of radical intermediates in the photodecompositions of water at TiO_2 particulate systems. *J Phys Chem* 1979;83:3146–51.
- [121] Barb WG, Baxendale JH, George P, Hargrave KR. Reactions of ferrous and ferric ions with hydrogen peroxide. *Trans Faraday Soc* 1951;47:462–500.
- [122] Bielski BHJ. Fast kinetic studies of dioxygen-derived species and their metal-complexes. *Phil Trans Roy Soc Lond B* 1985;311:473–82.
- [123] Armstrong D. Free radicals in molecular biology, aging and disease. New York, NY: Raven Press; 1984.
- [124] Janzén EG, Wang YY, Shetty RW. Spin-trapping with α -(4-pyridyl-1-oxide)-N-tert-nitylnitrone in aqueous solutions: a unique electron spin response spectrum for the hydroxyl radical adduct. *J Am Chem Soc* 1978;100:2923–5.
- [125] Tengvall P, Lundström I, Sjöqvist L, Elwing H, Bjursten LM. Titanium-hydrogen peroxide interaction: model studies of the influence of the inflammatory response on titanium implants. *Biomaterials* 1989;10:166–75.
- [126] Pan J, Thierry D, Leygraf C. Electrochemical and XPS studies of titanium for biomaterial applications with respect to the effect of hydrogen peroxide. *J Biomed Mater Res* 1994;28:113–22.
- [127] Bianchi G, Malaguzzi S. Cathodic reduction of oxygen and hydrogen peroxide on titanium. Proceedings of the first international congress on metallic corrosion London, April 10–15. 1961. pp. 78–83.
- [128] Pan J, Thierry D, Leygraf C. Hydrogen peroxide toward enhanced oxide growth on titanium in PBS solution: Blue coloration and clinical relevance. *J Biomed Mater Res* 1996;30:393–402.
- [129] Pan J, Liao H, Leygraf C, Thierry D, Li J. Variation of oxide films on titanium induced by osteoblast-like cell culture and the influence of an H_2O_2 pretreatment. *J Biomed Mater Res* 1998;40:244–56.
- [130] Albrektsson T. The response of bone to titanium implants. *CRC Crit Rev Biocompatibility* 1984;1:53–84.
- [131] Bearinger JP, Orme CA, Gilbert JL. Effect of hydrogen peroxide on titanium surfaces: *in situ* imaging and step-polarization impedance spectroscopy of commercially pure titanium and titanium, 6-aluminum, 4-vanadium. *J Biomed Mater Res* 2003;67A:702–12.
- [132] Oshida Y, Tuna EB. Science and technology integrated titanium dental implant systems. In: Basu B, Katti D, Kumar A, editors. *Advanced biomaterials*. Wiley; 2009. p. 143–77.
- [133] Ramazanoglu M, Oshida Y. Osseointegration and bioscience of implant surfaces—current concepts at bone—implant interface. In: Turkyilmaz I editor. *Dental Implant/Book I* InTech Pub; 2011. pp. 57–82.
- [134] Tomsia A, Launey ME, Lee JS, Mankani MH, Wegst UGK, Saiz E. Nanotechnology approaches to improve dental implants. *Int J Oral Maxillofac Implants* 2011;26:25–44.
- [135] Bae IH, Yun KD, Kim HS, Jeong BC, Lim HP, Park SW, et al. Anodic oxidized nanotubular titanium implants enhance bone morphogenetic protein-2 delivery. *J Biomed Mater Res B Appl Biomater* 2010;93:484–91.
- [136] Balasundaram G, Yao C, Webster TJ. TiO_2 nanotubes functionalized with regions of bone morphogenetic protein-2 increases osteoblast adhesion. *J Biomed Mater Res A* 2008;84:447–53.
- [137] Brammer KS, Oh S, Frandsen CJ, Jin S. TiO_2 nanotube structures for enhanced cell and biological functionality. *J Met* 2010;62:50–5.

- [138] Yu WQ, Qiu J, Zhang FQ. *In vitro* corrosion study of different TiO₂ nanotube layers on titanium in solution with serum proteins. *Colloids Surf B Biointerfaces* 2011;84:400–5.
- [139] Sul YT. Electrochemical growth behavior, surface properties, and enhanced *in vivo* bone response of TiO₂ nanotubes on microstructured surfaces of blasted, screw-shaped titanium implants. *Int J Nanomed* 2010;5:87–100.
- [140] Cui CX, Gao X, Qi YM, Liu SJ, Sun JB. Microstructure and antibacterial property of *in situ* TiO(2) nanotube layers/titanium biocomposites. *J Mech Behav Biomed Mater* 2012;12:178–83.
- [141] Feng XJ, Macak JM, Albu SP, Schmuki P. Electrochemical formation of self-organized anodic nanotube coating on Ti–28Zr–8Nb biomedical alloy surface. *Acta Biomater* 2008;4:318–23.
- [142] Xin Y, Jiang J, Huo K, Hu T, Chu PK. Bioactive SrTiO(3) nanotube arrays: strontium delivery platform on Ti-based osteoporotic bone implants. *ACS Nano* 2009;3:3228–34.
- [143] Hori N, Ueno T, Takeuchi K, Tsukimura N, Yamada M, Hattori M, et al. Selective cell affinity of biomimetic micro-nano-hybrid structured TiO₂ overcomes the biological dilemma of osteoblasts. *Dent Mater* 2010;26:275–87.
- [144] Wu X, Lui X, Wei J, Ma J, Deng F, Wei S. Nano-TiO₂/PEEK bioactive composite as a bone substitute material: *in vitro* and *in vivo* studies. *Int J Nanomed* 2012;5:1215–25.
- [145] Zhang Z, Sun J, Hu H, Wang Q, Lui X. Osteoblast-like cell adhesion on porous silicon-incorporated TiO₂ coating prepared by micro-arc oxidation. *J Biomed Mater Res B Appl Biomater* 2011;97:224–34.
- [146] Park JW, Kim YJ, Jang JH, Song H. Osteoblast response to magnesium ion-incorporated nanoporous titanium oxide surfaces. *Clin Oral Implants Res* 2010;21:1278–87.
- [147] Narayan R. Recent development in electronic, functional, and biological thin films. *J Met* 2012;58:505.
- [148] Narayan R, Monteiro-Riviere NA, Brigmon RL, Pellin MJ, Elam JW. Atomic layer deposition of TiO₂ thin films on anoporous alumina template: medical applications. *J Met* 2009;61:12–6.
- [149] Hu H, Zhang W, Qiao Y, Jiang X, Liu X, Ding C. Antibacterial activity and increased bone marrow stem cell functions of Zn-incorporated TiO₂ coatings on titanium. *Acta Biomater* 2012;8:904–15.
- [150] Schvenoz CE, Alterach MA, Vera ML, Rosenberger MR, Ares AE. Characteristics of hemocompatible TiO₂ nano-films produced by the sol–gel and anodic oxidation techniques. *J Mater* 2010;62:84–7.
- [151] Aäritalo V, Areva S, Jokinen M, Lindé M, Peltola T. Sol–gel TiO(2)–SiO(2) implant coatings for direct tissue attachment. Part I: design, preparation and characterization. *J Mater Sci Mater Med* 2007;18:1863–73.
- [152] Haghighi S, Khorrami SA, Nabatchian A. Preparation and characterization of self-cleaning TiO₂ nanofilm on quartz substrate using sol–gel spin coating technique. <http://www.civilica.com/EnPaper-NCNN01-NCNN01_410.html/>.
- [153] Joya Y, Wang T, Liu Z. Formation and antibacterial activities of nanostructured TiO₂ thin films by sol–gel/laser-induced technique. <<https://www.escholar.manchester.ac.uk/uk-ac-man-scw:144832/>>

- [154] Zhou XS, Li LJ, Lin YH, Nan CW. Characterization and properties of anatase TiO₂ film prepared via colloidal sol method under low temperature. *J Electroceramics* 2008;21:795–7.
- [155] Jeong SH, Park YJ, Kim BS, Song HJ. Effects of oxygen on bioactivity of titanium oxide films fabricated by electron beam evaporation. *J Nanosci Nanotechnol* 2007;7:3815–8.
- [156] Popescu S, Demetrescu I, Sarantopoulos C, Gleizes AN, Iordachescu D. The biocompatibility of titanium in a buffer solution; compared effects of a thin film of TiO₂ deposited by MOCVD and of collagen deposited from a gel. *J Mater Sci Mater Med* 2007;18:2075–83.
- [157] Ueno T, Yamada M, Hori N, Suzuki T, Ogawa T. Effect of ultraviolet photoactivation of titanium on osseointegration in a rat model. *Int J Oral Maxillofac Implants* 2010;25:287–94.
- [158] Ahn SJ, Han JS, Lim BS, Lim YJ. Comparison of ultraviolet light-induced photocatalytic bacterial effect on modified titanium implant surfaces. *Int J Oral Maxillofac Implants* 2011;26:39–44.
- [159] Harmankaya N, Igawa K, Stenlund P, Palmquist A, Tengvall P. Healing of complement activating Ti implants compared with non-activating Ti in rat tibia. *Acta Biomater* 2012;8:22–6.
- [160] Daro T. Bones made of titanium. *J Met* 2012; <<http://www.asminternational.org/portal/site/mpmd/News/>>

This page intentionally left blank

5 Mechanical and Tribological Behaviors

5.1 Introduction

Biomechanics includes all facets of musculoskeletal, cardiovascular, respiratory, implant–tissue interface, mechanics of prostheses, and mechanisms of chewing. Given such a wide range of coverage, the area of interest becomes much narrower when considering titanium applications only. Simultaneously, however, biomechanics is a multidisciplinary field, requiring various basic knowledge including statics and dynamics, elasticity and plasticity, fatigue, fracture mechanics, fracture toughness, and tribological actions (in terms of surface metrology, contact mechanics, friction, lubricant, and wear). Materials in bioengineering can range widely from very small (such as a virus or bacteria) to very large and complex sizes, including of course a healthy human body. They also cover the various products manufactured by using the methodologies in connection with biological disciplines. Limbs of vertebrate animals have synovial joints. Many arthropod joints and the hinges of bivalve mollusks owe their mobility to components that bend, rather than to surfaces that slide over each other. Peak forces on animal joints tend to be roughly proportional to (body mass)^{2/3} [1].

Based on the above argument, in this chapter, fatigue, fracture, and biotribological actions, such as friction and wear as well as wear debris toxicity, will be discussed.

Recently, a new term “tribocorrosion” (corrosion phenomenon under influences of tribological or biotribological action) has been introduced and is discussed in Chapter 3 in this second edition. In tooth systems, deterioration of hard tooth tissues, most often because of attrition and caries processes, makes normal functioning of stomatognathic systems much difficult, due to severe biotribological action. Although tribology intraoral environment should be obviously indispensable, it is beyond the scope of this book.

5.2 Fatigue

Fatigue is the loss of strength and other important properties as a result of stressing over a very long period of time. Fatigue is very important, as it is the single largest

cause of failures in metals (estimated as about 90% of metallic failures); polymers and ceramics are also susceptible to this type of failure. Fatigue is a very general phenomenon in most materials and even living organisms. The word “Fatigue” is originally from Latin “Fatigare.” The term itself is derived from fatigue meaning “to tire.” The root “fati” refers literally to an opening or yawning phenomenon vividly descriptive of fatigue in people, and especially in view of ubiquity of crazing and cavitation, in materials as well [2].

Fatigue has often been observed in Ti and Ti alloys and is considered as an important cause of the failure of the materials. For example, fatigue failure has been reported in dental implants [3], removable partial denture (RPD) framework [4], clasps [5,6], plates, pedicle screws, and cables [7–10]. The cyclic loading applied to orthopedic implants during body motion results in an alternating localized plastic deformation of microscopically small zones of stress concentration produced by notches or microstructural inhomogeneities [10]. Mechanical environment related to fatigue may be divided into two distinct groups: strain-controlled and stress-controlled.¹ Although most fatigue environments in the human body are a combination of the two, the highly compliant nature of biological materials tends to place them toward the direction of strain-controlled fatigue [11]. Examples of strain-controlled applications include pacemaker leads, which require a conductive metal that can survive very high numbers of flexing motions without breaking, and clasps of RPD, which require adequate retention for insertion and removal of the device [12]. Lin et al. [13] employed the tension-to-tension stress mode for fatigue tests on titanium materials (CpTi, Ti–13Nb–13Zr, Ti–6Al–4V, and Ti–7.5Mo) in air under R (stress ratio = $\sigma_{\min}/\sigma_{\max}$) of 0.1, with frequency of 10 Hz. It was found that (i) Ti–6Al–4V and CpTi have higher stress-controlled fatigue resistance, but lower strain-controlled fatigue resistance than Ti–7.5Mo and Ti–13Nb–13Zr, (ii) Ti–7.5Mo demonstrates the best strain-controlled fatigue performance, and (iii) the fatigue cracks almost always initiate from casting-induced surface/subsurface pores [13].

Clasps undergo permanent deformation to cause fatigue fracture under repeated flexures during denture insertion and removal, and masticatory actions [14–17]. The fatigue life of cast clasps made of CpTi was reported to be shorter than that of Co–Cr and gold alloy clasps [12]. However, the fatigue fracture and permanent deformation of cast clasps made of Ti-based alloy have not been sufficiently assessed in relation to stress distribution, and little is known about how these clasps

¹ Stress-controlled fatigue test is conducted in such a way that repeated load is controlled between predetermined upper and lower stress levels. If the tested material is fully annealed to start with and a work-hardening type, the material's strength increases by repeated stressing. Hence, the severity of fatigue process is getting milder. On the other hand, if the starting material's condition is a work-softening type, its original strength decreases by cycles, resulting in shortening fatigue life. On the contrary, by the strain-controlled fatigue testing, each cycle is controlled between preset upper and lower strain. If the fully annealed and work-hardening material is tested under the strain-controlled fatigue mode, because the material strength increases by cyclic loading, the applied stress needs to increase to maintain the preset level of upper strain. On the other hand, by the work-softening type materials, applied stress level decreases.

would function in long-term clinical use. Permanent deformation and fatigue fracture are caused by the stress created in the clasp [18,19]. The stress distribution may depend on the elastic modulus of the alloy, dimensions and curvature of the clasp [20,21], and amount and direction of deflection in relation to the abutment undercut [22]. Mahmoud et al. [23] investigated the gold alloy and Ti–6Al–7Nb which were subjected to cyclic deflection of preset values of 0.25 mm, 0.50 mm, and 0.75 mm for 10^6 cycles. It was concluded that the gold alloy (70Au–4.4Pt–13.5Ag–8.8Cu–2Pd–0.1Ir) clasps exhibited significantly longer fatigue lives, while the Ti–6Al–7Nb clasps showed significantly greater resistance to permanent deformation under cyclic deflection [23].

The fatigue resistances of experimentally prepared NiTi (50.8%Ni–49.2%Ti) cast clasps as well as CpTi, Co–Cr alloy, and Au–Ag–Pd–Cu alloy clasps were evaluated in a simulated clinical situation [5]. The change in force required to remove the NiTi clasps was recorded under a repeated placement-removal test on steel model abutment teeth. The tips of the clasps were located in the 0.25 mm and 0.5 mm undercut area of the abutments. It was found that (i) no significant change in the retentive force was found in NiTi clasps in the 1010 repeated cycles, but (ii) the other three types of clasps revealed a significant decrease in the force required for removal during the test, suggesting that the cast NiTi clasp may be suitable in removable prosthodontic constructions because of its significantly less permanent deformation during service [5].

The fatigue failure of hip joint prostheses will be expected to assume more importance in second-generation implants aimed at younger, more active patients. Furthermore, new designs and material combinations including coatings (e.g., hydroxyapatite) may introduce fatigue problems that as of yet have not been considered. Styles et al. [24] conducted corrosion-fatigue tests on a model four-point bendbar test piece (milled-annealed Ti–6Al–4V) in a physiological solution (i.e., Ringer's solution) at 37°C. It was found that the introduction of superimposed block overload (50 cycles) to signify stair ascent/descent of fast walking and single overloads to signify fit/stand movements or stumbling were found to reduce fatigue life by >50% [24].

CpTi (grade II) Nd:Yag laser weldment was subjected to fatigue cycling at a stress ratio of $R = -1$ under the frequency of 10 Hz. The tests were conducted in synthetic saliva (pH:7) and fluoride synthetic saliva (pH:7) with NaF of 1000 ppm or 2.223 g/1000 mL, compared to in-air tests. It was concluded that (i) the laser-welding procedure significantly reduced the fatigue life of CpTi and Ti–6Al–4V alloy specimens, and (ii) synthetic saliva and fluoride saliva adversely affected fatigue life compared with the control in air tests [25].

Surface roughness of cast CpTi and Ti–6Al–4V was evaluated when they were submitted to conventional or electrolytic polishing, correlating the results with corrosion-fatigue (10 Hz, $R = 1$, indicating that the test was conducted in tension–tension mode) at strength testing performed in artificial fluorided saliva. Specimens were also tested in air at room temperature to evaluate the effectiveness of the corrosion-fatigue test model. It was found that (i) electrolytic polishing (5%HF–35%HNO₃–60%H₂O) provided lower surface roughness (0.24 μm) than

conventional polishing using titanium polishing paste (0.32 μm), (ii) regardless of the polishing conditions, surface roughness of Ti–6Al–4V (0.25 μm) was lower than that of CpTi (0.31 μm), and the fluoridated environment did not influence fatigue performance, and (iii) there was no correlation between fatigue performance and surface roughness. Based on these findings, it was concluded that surface roughness of Ti–6Al–4V was lower than CpTi. For cast Ti frameworks, the electrolytic polishing regimen was found to be more effective than the manufacturer's polishing instructions with abrasives and rotary instruments. After polishing, it was found that differences in surface roughness values did not affect corrosion-fatigue performance [26].

It is widely understood that the mechanical properties of titanium alloys are very sensitive to the characteristics of the microstructure. The type of phases, grain size and shape, morphology, and distribution of the fine microstructure ($\alpha + \beta$ phases) determine the properties and therefore the application of titanium alloys [27]. Microstructural modification by thermomechanical treatment is widely used to optimize the properties of high-strength titanium alloys for specific applications. However, because the surface of a mechanically loaded titanium part often experiences different conditions than the bulk, it makes sense in many applications to modify only the surface microstructure. By combining thermal treatments with mechanical working, stability of the resulting tailored surface is enhanced. Such stability is especially significant for resistance to fatigue crack nucleation and growth. Akahori et al. [28] found that, for Ti–6Al–7Nb alloy, by increasing the volume fraction of the primary α -phase from 0 to 70%, the fatigue limit is raised. It was also reported that changing the cooling rate after solution treatment from air cooling to water quenching improved the fatigue limit Ti–6Al–7Nb alloy significantly [28], due to increased surface layer hardness.

Koahn et al. [29] used acoustic emission (AE) phenomenon to record AE events and event intensities (e.g., event amplitude, counts, duration, and energy counts) and analyzed these parameters during fatigue loading of uncoated and porous-coated Ti–6Al–4V alloy. AE provides the ability to spatially and temporally locate multiple fatigue cracks in real time. Fatigue of porous-coated Ti–6Al–4V is governed by a sequential fracture process of transverse fracture in the porous coating $\rightarrow$ sphere/sphere and sphere/substrate debonding $\rightarrow$ substrate fatigue crack initiation $\rightarrow$ slow and rapid substrate fatigue crack propagation. Because of the porosity of the coating, the different stages of fracture within the coating may occur in a discontinuous fashion. Therefore, the AE events generated are intermittent and the onset of each mode of fracture in the porous coating can be detected by increases in AE events rate. Changes in AE events rate also correspond to changes in crack extension rate, and may therefore be used to predict failure. It was mentioned that (i) the magnitude of the AE event intensities increased with increasing fracture and microvoid coalescence generated the highest AE event amplitudes (100 dB), whereas plastic flow and friction generated the lowest AE event amplitudes (55–65 dB), and (ii) fractures in the porous coating can be characterized by AE event amplitude of less than 80 dB [29].

There are several ways to improve fatigue strength, including modifying surface roughness and hardness and surface residual stress magnitude, and altering materials design, as well as surface coating. Mechanical surface treatment such as shot peening, polishing, or surface rolling can improve the endurance limit in titanium-based materials, but the changes they induce can have contradictory influences on fatigue strength. For example, surface roughness determined whether fatigue strength is primarily crack-nucleation controlled (smooth) or crack-propagation controlled (rough). For smooth surfaces, a work-hardened surface layer can delay crack nucleation because of its increase in strength. But on rough surfaces, a work-hardened surface layer cannot retard crack propagation because of its reduced ductility. However, near-surface residual compressive stresses significantly retard crack growth whether the surface is smooth or rough. It was also reported that by grain refining of Ti–8Al alloy, the fatigue strength is improved to 325 MPa, compared to a coarse grain of 275 MPa at 10^6 cycles [30,31].

A new surface-coating method by which CaP invert glass is used to improve the bioactivity of titanium alloys has been developed recently [32]. In this method, the powder of CaP invert glass ($\text{CaO}-\text{P}_2\text{O}_5-\text{TiO}_2-\text{Na}_2\text{O}$) is coated on the surface of titanium alloy samples and heated between 800°C and 850°C. With this treatment, a calcium phosphate layer mainly containing $\beta\text{-Ca}_3(\text{PO}_4)_2$ phase can be coated easily on titanium alloy samples. The effect of such coating was evaluated on the fatigue properties of Ti–29Nb–13Ta–4.6Zr (a new metastable β -alloy for biomedical applications). It was reported that the fatigue endurance limit of the coated alloy was found to be about 15% higher than that of uncoated alloy as a result of the formation of a hard ($\alpha + \beta$) layer and a small amount of the ω -phase during the coating process, (ii) the coating exhibits excellent adhesion to the substrate during the tensile and fatigue tests, and (iii) subsequent aging at 400°C for 3 days greatly improves the fatigue resistance of the coated alloy due to isothermal ω -phase precipitation [32].

5.3 Fretting

Fretting is a poorly understood form of fatigue caused by minute oscillating motions between materials in rubbing contact. Fretting refers to wear and sometimes corrosion damage at the asperities of contact surfaces. This damage is induced under load and in the presence of repeated relative surface motion, as induced for example by vibration. The ASM Handbook on Fatigue and Fracture defines fretting as: “A special wear process that occurs at the contact area between two materials under load and subject to minute relative motion by vibration or some other force.” The amplitude of the relative sliding motion is often in the order from micrometers to millimeters, but can be as low as 3–4 nm. The contact movement causes mechanical wear and material transfer at the surface, often followed by oxidation of both the metallic debris and the freshly exposed metallic surfaces. Because the oxidized debris is usually much harder than the surfaces from which it

came, it often acts as an abrasive agent that increases the rate of both fretting and a mechanical wear called false brinelling. It was first observed in press-fitted joints, but it can be expected to arise even under light pressures between parts of equipment designed for operation in high vacuum, for example, in a lunar surface vehicle [33]. The small cyclic movements under pressure result in extensive and very characteristic surface damage through formation of powdery debris (often composed of oxides) with cracks developing at a later stage. It is an attrition due to oscillatory relative motion of small amplitude (30–150 μm) in metal-to-metal systems [34].

Corrosion-resistant material may not necessarily be biocompatible, and more biocompatible material may be less corrosion resistant. Especially fretting corrosion may represent a problem in articulating devices like knee joints or plate/screw systems. It is therefore necessary to investigate, in number of details, materials aimed for medical purposes. Tribological approach is important in that process [35]. In dental and medical environment, it is rare that mechanical fretting takes place on its own; rather, it is very commonly accompanied by corrosion action—so-called fretting corrosion. Yu et al. [36] studied the radial fretting behavior of cortical bone against CpTi (grade II) balls. It was reported that (i) the damages of cortical bone aggravated with increase in the normal loads and cycles, and (ii) cracks propagation on the surface of cortical bone was observed along the cement line as the most popular cases. Torsional fretting wear on Ti–6Al–7Nb alloy was also conducted when the surface was treated with nitrogen gas plasma immersion ion implantation deposition [37]. The test of untreated and nitrogen-ion-implanted Ti–6Al–7Nb was carried out under simulated physiological conditions (serum solution) in a torsional fretting wear test device. It was concluded that (i) ion implantation layering can improve resistance to torsional fretting wear and thus has wide potential application for the prevention of torsional fretting damage in artificial implants, and (ii) an increase in ion implantation concentration inhibited detachment by delamination action [37].

Recently, Clemens et al. [38], investigating the rotational fretting wear of Ti–6Al–4V flat against silicon nitride (Si_3N_4) ceramics ball using a special rotational fretting wear test apparatus, reported that (i) the micro-examination of the wear scars revealed an accumulation of plastic deformation within the center of the wear scars in the gross slip conditions, and (ii) the mechanisms for fretting wear were quite different in the different fretting regimes [38].

5.4 Fracture and Fracture Toughness

The ideal biomaterial for implant applications, especially for joint replacements, is expected to exhibit excellent properties such as no adverse tissue reactions, excellent corrosion resistance in the body fluid medium, high mechanical strength and fatigue resistance, low modulus, low density, and good wear resistance [39]. As for searching V-free Ti-based alloys, Ti–6Al–7Nb and Ti–5Al–2.5Fe were

developed for orthopedic applications. These two alloys exhibited mechanical properties similar to Ti–6Al–4V and were primarily developed in response to concerns of potential cytotoxicity and adverse tissue reactions caused by V [40,41]. Further studies have shown the release of both V and Al ions from Ti–6Al–4V alloy might cause long-term health problems, such as peripheral neuropathy, osteomalacia, and Alzheimer's disease [42,43].

The fracture behavior of the two cast Ti materials was investigated by AE analysis during the fracture toughness testing. Specimens for the test were cast by the lost wax method using a specially designed Ti casting machine of pressure-different method for dental use. A fatigue crack was inserted from the machined notch tip into the body of a specimen in the range of 0.45–0.55 a/W. AE signals released during the fracture toughness tests were detected by two sensors attached to both ends of the specimen. It was found that (i) from the early stage of the fracture toughness tests, AE signals started to be released in all types of specimens, and (ii) a reaction layer with the investment materials of about 50–100 μm was thought to be the result of the AE release from an early stage of the fracture toughness test [44].

The mechanical properties of titanium alloys strongly depend on their phase composition and structure, which result from casting and/or thermomechanical processing, and can be significantly influenced by the following heat treatment. Treatments that include heating into the β -phase, which would provide full transformation of the as-received microstructure, are not commonly used because of a fast grain growth in the β -phase. This drawback leads to significant deterioration of the mechanical properties. Moreover, large β -grains are typically associated with the formation of coarse-grained structures by both martensitic $\beta \rightarrow \alpha$ or diffusional $\beta \rightarrow (\alpha + \beta)$ transformations on cooling. It was shown that a significant improvement in the mechanical properties of high-strength titanium alloys can be reached by using a special heat treatment based on rapid heating into the β -region. Such a treatment allows the production of a high-temperature β -phase with a fine-grained microstructure and optimal chemical inhomogeneity, which strongly determines the mechanism and kinetics of phase transformations on cooling and further annealing or aging. A wide range of final microstructures with an enhanced combination of mechanical properties can be obtained [45].

Banerjee et al. [39] evaluated Ti–34Nb–9Zr–8Ta and Ti–13Mo–7Zr–3Fe for their heat-treatment capabilities. In the homogenized condition, both alloys exhibited a microstructure consisting primarily of a β -matrix with grain boundary α -precipitates and a low-volume fraction of intra-granular α -precipitates. On aging, the homogenized alloys at 600°C for 4 h, both alloys exhibited the precipitation of refined scale secondary α -precipitates homogeneously in the β -matrix. It was reported that, while the hardness of the Ti–Mo–Zr–Fe alloy marginally increased, the hardness of Ti–Nb–Zr–Ta alloy decreased substantially as a result of the aging treatment [39].

Ti single-crystal planes of different atomic density have been reported to show different oxidation characteristics, as discussed in Chapter 4. The differences in oxide characteristics have further been demonstrated to lead to differences in

osteoblast attachment. Mante et al. [46] investigated the preferred crystallographic planes of titanium for osteoblast attachment in order to optimize the surfaces of single-crystal and polycrystalline titanium implants for anchoring various prostheses. Nanoindentation techniques were used to determine mechanical properties of two crystallographic planes of Ti of different atomic density. It was reported that (i) modulus of elasticity (MOE) of 128 GPa was obtained for polycrystalline Ti and 123 GPa and 124 GPa for the basal and pyramidal planes, respectively, (ii) the variation of MOE with crystal orientation was not greater than the statistical variation in the data, (iii) surface hardness values were 2.1 GPa for polycrystal and 1.6 GPa and 1.9 GPa for basal and pyramidal planes, respectively, and (iv) hardness depth profile (0–2000 nm) showed a sharp increase at shallow depths and may reflect changes caused by oxidations of the Ti surfaces [46].

It has been found that every machining operation produces a distinctive residual stress in the surface layer. When any metallic material is subjected to wire drawing, cutting, pressing, or rolling, there will be a residual strain, which is normally relieved by an annealing process. If such residual strain is not removed, the grains become distorted. Distorted microstructures, having higher values of dislocation density, decrease the plastic formability under repeated stressing, causing a premature crack. When titanium wire is formed to manufacture dental implants by the wire-drawing process, the work strain can remain in the entire microstructure. Besides, if cutting is further performed, relatively large amounts of residual strain would remain. It is reported that heating at 600°C for 1 h is an optimum stress relief heat treatment for CpTi (grade II) without any remarkable grain coarsening [47]. Residual stress is not always adverse; rather, it should be beneficial if it is compressive residual stress, so that cracks tend to close and applied stress can increase. Rolling (creating surface compressive residual stress) alone increases the notched fatigue limit from the low value of 400 MPa to 1100 MPa [30,31].

5.5 Biotribological Actions

5.5.1 *In General*

Biotribology is a compound word of biology and tribology. In 1966, the term “tribology” was introduced, from the Greek word $\tau\rho\iota\beta\omicron\sigma$ (to rub), defined as the science and technology dealing with friction, wear, and lubrication.²

Tribology is the science dealing with the interaction of surfaces in tangential motion. Hence, tribology includes the nature of surfaces from both a chemical and

² The prefix “tri” normally refers to “three” in those words, such as “tripot,” “trigonometry,” “trilingual,” and “trifocal.” At the same time, we just know that tribology is a science about three phenomena (friction, wear, and lubrication), so that it is easily misinterpreted that the tribology is a science dealing with the aforementioned three phenomena, but this is not true. The Greek word $\tau\rho\iota\beta\omicron\sigma$ does not have a prefix meaning “three.” This is just a matter of coincidence.

physical point of view, including topography, the interaction of surfaces under load, and the changes in the interaction when tangential motion is introduced. Macroscopically, the interactions are manifested in the phenomena of friction and wear. Modification of the interaction through the interposition of liquid, gaseous, or solid films is known as the lubrication process. Hence, from a macroscopic point of view, tribology includes lubrication, friction, and wear [48]. There are four major clinical reasons to remove the implants: (1) fracture, (2) infection, (3) wear, and (4) loosening. Among these, the removal due to the infection generally occurs in relatively early stages after implantation, while the other three incidents typically increase gradually by years, because they are somewhat related to biotribological reactions. Human joints are one example of natural joints, and show low wear and exceedingly low friction through efficient lubrication. Disease or accident can impair the function at a joint, and this can lead to the necessity for joint replacement [48].

Special tribological element problems arise in many mechanical devices used in various areas, for example, computer devices and medical implants (prostheses, assists, and artificial organs). Medical implants, such as prostheses, should demonstrate very good tribological properties, as well as biological inertness. Their longevity depends significantly on the wear of the rubbing elements and must be extended as much as possible. The developments of total replacement of hip, knee, ankle, elbow, shoulder, and hand joints (and the appropriate surgical techniques) have been the major success of orthopedic surgery, and would not have been possible without extensive *in vitro* and *in vivo* studies of the tribological problems, especially wear, associated with such artificial joints.

There are a number of important biotribological testing parameters that can greatly affect the outcome of a wear study in addition to the implant design and material selection. The current American Society of Testing and Materials and International Organization for Standardization wear testing standards for spine arthroplasty leave many choices as to testing parameters including but not limited to sequence of kinematics and load, phasing, type of lubricant, and specimen preparation (sterilization and artificial aging) [49]. *In situ* techniques of optical microscopy and Raman spectroscopy were used to observe interfacial sliding dynamics and identify near-surface structural and chemical changes. Third-body physical and chemical processes, such as thickening, thinning, loss of transfer films, generation of wear debris, and sliding-induced chemical changes, were identified for sapphire against Ti–Si–C, nanocrystalline diamond, and titanium- and tungsten-doped diamond-like carbon coatings. These processes observed by *in situ* methods were also used to explain why friction and wear behavior changed with coating composition, properties, or test conditions [50].

5.5.2 Friction

Zwicker et al. [51] investigated the friction behavior of a hip prosthesis head fabricated from Ti–5Al–2.5Fe alloy in contact with an ultrahigh molecular weight polyethylene (UHMWPE) cup. It was shown that (i) the frictional behavior of a head coated with an oxide layer about 1–3 μm thick produced by induction heating

of the surface was equal to that of a head fabricated from alumina ceramic, (ii) the oxide layer was still present after 10^7 cycles under maximum load of 3200 N in 0.9% NaCl solution, and (iii) examination of the microstructure of the oxide layer after testing showed that it was unchanged by friction test under overload service conditions. Therefore, the production of such oxide layers on Ti and Ti alloy implants that are locally stressed by friction during service is recommended [51].

Another important incidence involving friction in dentistry is between the orthodontic bracket and archwires. While orthodontic mechanotherapy is active, sliding of bonded brackets along archwires occurs in all orthodontic cases. When these sliding movements occur, frictional forces between the archwire and the bracket are produced. Different combinations of materials have varying coefficients of friction, leading to different amounts of frictional force created within the bracket/archwire system. This force either retracts or protracts between brackets. It is thought that static, rather than kinetic, frictional forces may be more relevant in orthodontic tooth movement. This is due to the bracket/archwire system having stopping and starting movements as the teeth are moved. *In vitro* testing of orthodontic archwires and brackets can be performed in either a wet or dry environment. Wet testing is usually done by submerging the archwire/bracket system in saliva, salivary substitute, or glycerin solution. Stannard et al. [52] measured kinetic coefficients of friction for stainless steel, β -Ti, NiTi, and Co—Cr archwires on a smooth stainless steel or Teflon surface. A universal material testing instrument was used to pull rectangular archwire (0.17×0.025 in.²) through pneumatically controlled binding surfaces. Coefficients of friction were determined under dry and wet (artificial saliva) conditions. It was found that (i) frictional force values (and thus coefficients of friction) were found to increase with increasing normal force for all materials, (ii) β -Ti and stainless steel sliding against stainless steel, and stainless steel wire on Teflon, consistently exhibited the lowest dry friction values, (iii) artificial saliva increased friction for stainless steel, β -Ti, and NiTi wires sliding against stainless steel, but (iv) artificial saliva did not increase friction of Co—Cr, stainless steel sliding against stainless steel, or stainless steel wire on Teflon compared to the dry condition, and (v) stainless steel and β -Ti wires sliding against stainless steel, and stainless steel wire on Teflon, showed the lowest friction values for the wet conditions [52].

Stainless steel, Co—Cr, NiTi, and β -Ti wires were tested in narrow single (0.050 in.), medium (0.130 in.), and wide twin (0.180 in.) stainless steel brackets in both 0.018 and 0.022 in slots. It was reported that (i) β -Ti and NiTi wires generated greater amounts of frictional forces than stainless steel or Co—Cr wires did for most wire size, and (ii) increase in wire size generally resulted in increased bracket-wire friction [53]. However, it was reported that wires in ceramic brackets generated significantly stronger frictional forces than did wires in stainless steel brackets [54].

Kusy et al. [55] evaluated coefficients of friction in the dry and wet (saliva) states of stainless steel, Co—Cr, NiTi, and β -Ti wires against either stainless steel or polycrystalline alumina brackets. It was found that (i) in the dry state and regardless of slot size, the mean kinetic coefficients of friction were smallest for the all stainless steel combinations (0.14) and largest for the β -Ti wire combination

(0.46), (ii) the coefficients of polycrystalline alumina combinations were generally greater than the corresponding combinations that included stainless steel brackets, and (iii) in the wet state, the kinetic coefficients of the all stainless steel combinations increased to 0.05 over the dry state, but (iv) all β -Ti wire combinations in the wet state decreased to 50% of the values in the dry state [55].

Surface roughness and static frictional force resistance of orthodontic NiTi archwires along with β -Ti alloy wire, stainless steel and Co—Cr alloy wires were measured. It was found that (i) the Co—Cr alloy and the NiTi alloy wires exhibited the lowest frictional resistance, (ii) the stainless steel alloy and the β -Ti wires showed the highest frictional resistance, and (iii) no significant correlation was found between arithmetic average roughness and frictional force values [56]. Oshida et al. [57] conducted friction tests to compare the wet static frictional forces of low friction “colors” (surfaces of wires are colored by the anodizing process) of Ti—Mo alloy (TMA) archwires with archwires of other materials (stainless steel, NiTi, and uncoated TMA), and to test the effects of repetitive sliding. The results showed that uncoated TMA wires produce the highest wet static frictional forces in all cases. In most cases, NiTi wires produced the next highest force levels, followed by the colored TMA wires and then stainless steel. Repetition seemed to have little to no effect on all of the archwires with the exception of NiTi and uncoated TMA. NiTi wires showed a decrease in force values as the wire was subjected to more repetitions. Uncoated TMA, on the contrary, showed that more friction developed between runs and a trend toward increasing friction as the wire had repeated use [57]. It is then recommended that further studies are required to correlate types of oxide(s) formed on Ti surfaces to frictional behaviors.

5.5.3 Wear and Wear Debris Toxicity

Unlike dental implants, most orthopedic implants will be subjected to biotribological actions. Metal ions released from the implant surface are suspected of playing some contributing role in the loosening of hip and knee prostheses, which are substantially subjected to biotribological environments. Thompson and Puleo [58] demonstrated that sublethal doses of the ionic constituents of Ti—6Al—4V alloy suppressed expression of the osteoblastic phenotype and deposition of a mineralized matrix. Bone marrow stromal cells (which were cultured for 4 weeks) were harvested from juvenile rats and exposed to time-staggered doses of a solution of ion representing the Ti—6Al—4V alloy. It was reported that (i) Ti—6Al—4V solutions were found to produce little difference from control solutions for total protein or alkaline phosphatase levels, but strongly inhibited osteocalcin synthesis, and (ii) calcium levels were reduced when ions were added before a critical point of osteoblastic differentiation (between 2 and 3 weeks after seeding). Based on these findings, it was indicated that ions associated with the Ti—6Al—4V alloy inhibited the normal differentiation of bone marrow stromal cells to mature osteoblasts *in vitro*, suggesting that ions released from implants *in vivo* may contribute to implant failure by impairing normal bone deposition [58].

Although devices made of Ti–6Al–4V have been remarkably successful, primarily in orthopedic and dental applications, clinical reports have implicated the biological response to release metal from this class of metals as a cause of failure. Bianco et al. [59] hypothesized that in the absence of wear, the amount of titanium released is small and will preferentially accumulate in local tissues. One important implication is that measurable quantities of titanium in serum and urine that have been observed in clinical studies result from mechanically induced or mechanically assisted release phenomena. In order to test this hypothesis, titanium levels in various tissues and fluids of animals both with and without titanium implants was determined. Titanium fiber felts were implanted into the tibia of rabbits. At various time points, serum and urine samples were collected from these rabbits as well as from two groups of control rabbits. The samples were analyzed for titanium concentration using electrochemical absorption spectrophotometry. It was reported that titanium levels in serum and urine do not increase in comparison to controls up to 1 year after implantation [59].

In total joint replacement, a polished metal surface generally articulates against an UHMWPE counter-bearing surface. Metals used include 316L stainless steel, Co–Cr–Mo alloy, and Ti–6Al–4V alloy (particularly with a hardened N^+ ion implanted surface to form TiN layer). For long-term performance, it is desired to minimize friction and UHMWPE wear, and it is also desirable to minimize metal ion release, which results from constant removal and reformation of passive surface oxides and oxyhydroxides during articulation. It was reported that (i) the inert ceramic-bearing surfaces eliminate the oxidative wear of UHMWPE and Ti–6Al–4V, and are also resistant to potential three-body wear from bone cement debris or potential stray porous metal coating material, and (ii) ceramic materials (e.g., alumina and zirconia) are available only for total hip replacement. For total knee replacement, although it is difficult and expensive to manufacture a monolithic ceramic knee surface, surface coating such as plasma-sprayed alumina and zirconia, TiN and amorphous diamond-like coatings through Physical Vapor Deposition/Chemical Vapor Deposition methods, or nitrogen ion implantation and oxygen or nitrogen diffusion hardening can be applicable [60]. The wear of balls (of femoral stem implant) of nitrogen-ion-implanted CpTi and Ti–6Al–4V alloy bearings against cups (of acetabular component) of UHMWPE was investigated using a simulator to approximate the conditions of an artificial hip joint. It was found that (i) differences in polymer wear rates related to variations in the surface finish of the balls, but not to ion implantation, were observed, (ii) the wear resistance of the femoral heads was significantly improved by the ion implantation, (iii) after one million cycles in the simulator (which is equivalent to approximately one year's use of a hip prosthesis in a patient), significant parts of the ion implanted layer had worn off on parts of the specimen, and (iv) this metallic wear was more extensive with the CpTi samples than with those of Ti–6Al–4V [61].

Ti–6Al–7Nb disks were subjected to pin-on-disk wear tests against the high-fusing porcelain which is normally used as denture teeth. The wear test was interrupted at 10,000, 50,000, 100,000, 150,000 and 200,000 cycles for X-ray diffraction examination. Two planes, (010) and (011), were chosen for investigating the

progressive wear damage characterization. It was found that (i) the plane (010) showed more sensitiveness than the plane (011) to the step-wise wear damage, (ii) the half-value width of the plane (010) showed continuously line-broadening, indicating either or both of nonuniform microstrain increasing and particle size decreasing, (iii) the plane (010) shifted toward higher 2θ angle (or lower d-spacing), indicating that crystalline grain was distorted during the wear action [62].

Metallic particles are clearly cytotoxic *in vitro*, whether produced from titanium-based [63–66] or cobalt–chromium alloys [63,67,68]. This cytotoxicity is probably secondary to intracellular dissolution at low pH levels, since it can be affected by blocking H^+ release [69]. Discussions of biological response to wear debris have tended to emphasize the number of particles produced by a device in a period of time or, occasionally, the total weight or rate of production (by weight) of the debris. The *in vitro* investigations of macrophage response to small particles suggest that the total surface area of the debris may be an important parameter [70]. Wear debris particle size, produced by adhesion, tends to vary inversely with material rigidity (i.e., MOE), thus metallic and ceramic materials can be expected to produce smaller particles than the polyethylene debris released by conventional bearings [71].

A recent study comparing the induction of macrophage apoptotic cell death by alumina, zirconia, and polyethylene particulates found the response to be concentration and size dependent, and particle composition (alumina, zirconia, or polyethylene) had no effect [72]. However, in a rabbit model, Kubo et al. [73] found marked histiocytic response around particles of UHMWPE (11 μm), stainless steel (3.9 μm), and Co–Cr (3.9 μm). A significant reduction in the histiocytic response was found surrounding particles of alumina ceramics (3.9 μm) and titanium (3.9 μm). Catels et al. [74] found that larger particles ($> 2 \mu\text{m}$) induced greater cell death than smaller particles, and inflammatory mediator (Tumor Necrosis Factor- α release) was significantly higher with polyethylene particles when compared to alumina and zirconia. Osteolysis has been reported in association with ceramic wear debris. Yoon et al. [75] performed total hip arthroplasties with insertion of a ceramic femoral head and acetabular component in 96 patients to determine the radiographic prevalence of osteolysis. It was reported that (i) 10 patients required revision with gross and microscopic evidence of surface wear, and (ii) histology and Scanning Electron Microscope analyses of the periprosthetic membrane demonstrated “abundant” ceramic wear particles with a mean particle size of 0.71 μm (in a range of 0.13–7.2 μm), supporting the concept that ceramic wear particles can stimulate a foreign-body response and periprosthetic osteolysis.

The fresh surface will be revealed due to the formation of fraction/wear products, and there may be a chemical reaction taking place between the freshly revealed surface of implants and the surrounding environments, as well as selective dissolution of the alloy constituents into the surrounding tissues. Additionally, it is generally believed that solid powders such as wear/friction products/particles cause an allergic reaction in the living tissue, so that the biological effects of wear products (debris) should be considered separately from the biocompatibility of the implants. Particulate wear debris is detected in histiocytes/macrophages of granulomatous tissues adjacent to loose joint prostheses. Such cell–particle interactions

have been simulated *in vitro* by challenging macrophages with particle doses according to weight percent, volume percent, and number of particles. Macrophages stimulated by wear particles are expected to synthesize numerous factors affecting events in the bone–implant interface. Wear debris from orthopedic joint implants initiates a cascade of complex cellular events that can result in aseptic loosening of the prosthesis [76]. Macrophages are cells which are mainly involved in phagocytosis and signaling and maintaining inflammation, which leads to cell damage in soft tissues and bone resorption [77,78]. The presence of large particles provides the major stimulus for cell recruitment and granuloma formation, whereas the small particles are likely to be the main stimulus for the activation of cells which release proinflammatory products. Apoptosis can be morphologically recognized by a number of features, such as loss of specialized membrane structures, blebbing, condensation of the cytoplasm, condensation of nuclear chromatin, and splitting of the cell into a cluster of membrane-bound bodies [77,78]. Recent advances in the understanding of the mechanisms of osteoclastogenesis and osteoclast activation at the cellular and molecular levels have indicated that bone marrow–derived macrophages may play a dual role in osteolysis associated with the total joint replacement: (1) the major cell in host defense responds to UHMWPE particles via the production of cytokines and (2) the precursors for the osteoclasts responsible for the ensuing bone resorption [79].

Luo et al. [80] synthesized titanium cement and formed a thin gradient titanium carbide coating on the Ti–6Al–4V substrate by using a novel sequential carburization under high temperature while the titanium cement femoral head was fabricated. The wear behavior of titanium cement femoral head was evaluated with an artificial joint hip simulator. It was reported that (i) the titanium cement femoral head could not only improve the wear resistance of an artificial femoral head but also decrease the wear of an UHMWPE joint cup, and (ii) the carburized titanium alloy femoral head could effectively control the UHMWPE debris distribution and increase the size of UHMWPE debris [80].

There is a unique study on tribology in cryogenic atmospheres [81]. It examined friction and wear behaviors of Ti–6Al–4V and Ti–5Al–4V–0.6Mo–0.4Fe alloys sliding against a tungsten carbide wheel under dry and cryogenic sliding conditions at different sliding speeds, loads, and distances. It was reported that (i) no substantial differences was observed between tribo-characteristics of both titanium alloys, (ii) under cryogenic sliding condition, tribo-characteristics were lower than those obtained under dry sliding, (iii) cryogenic sliding surprisingly gave higher friction coefficients, and (iv) under dry sliding, the main wear modes were adhesion and delamination, while, under cryogenic sliding, in addition to delamination, the abrasion wear mode dominated [81].

Majumdar et al. [82], studying the effect of heat treatment on the microstructure, hardness, and sliding wear behavior of Ti–13Zr–13Nb in dry as well as in wet conditions using Hank's solution and bovine serum as the lubricating media, found that (i) in Hank's solution, the wear rate of all the samples increased considerably, (ii) the wear process is characterized by ridged wear scars parallel to the sliding

direction with superficial plastic deformation along the sliding and smeared wear surface, and (iii) the wear mechanism was mainly abrasive [82].

5.6 Improvement for Antitribological Deterioration

To avoid such wear debris toxicity, the wear resistance is needed to be improved. Güleriyüz et al. [83] performed a comparative investigation of thermal oxidation treatment for Ti–6Al–4V to determine the optimum oxidation conditions for evaluation of corrosion-wear properties. Characterization of modified surface layers was made by means of microscopic examinations, hardness measurements, and X-ray diffraction analysis. Optimum oxidation condition was determined according to the results of accelerated corrosion tests made in 5 M HCl solution. It was reported that (i) Ti–6Al–4V alloy exhibited excellent resistance to corrosion after oxidation at 600°C for 60 h, and (ii) this oxidation condition achieved 25 times higher wear resistance than the untreated alloy during the reciprocating wear test conducted in a 0.9% NaCl solution [83].

CpTi was mirror polished and then abraded with waterproof polishing papers with SiC of different grit sizes (16 and 3 μm). When compared with the bulk, the interfacial zone was rich in oxygen and therefore subjected to high coherency strain, which was introduced to relieve the great lattice mismatch between the outer and inner layers of titanium substrate. It was reported that effects of solute oxygen hardening and strain hardening were speculated to be responsible for the surface hardening of both SiC-abraded surfaces. Accordingly, it was concluded that abrading with a coarse grit led to accumulation of a high, nonuniform strain in the titanium substrate, resulting in hardening of the surface layer [84].

Surface modification of biomaterials by conventional ion implantation and plasma immersion ion implantation are innovative methods to improve the biocompatibility of these advanced materials. Biocompatibility improvements of Ti–6Al–4V with N and O in a conventional implantation and a plasma immersion implantation process were evaluated. Tribocorrosion friction and wear tests were conducted in Hank's solution to investigate the aforementioned modifications. It was reported that the wear performance was only slightly improved due to a thin layer thickness, whereas, in contrast, the corrosion rate was significantly reduced [85].

For improving the antitribological phenomena, plasma-spray TiO₂ coating was evaluated [86]. A block-on-ring test device was used to investigate the tribological behavior of plasma-spray TiO₂ coating pairing with conventional metallic bearing materials. It was reported that (i) either triphenyl thiophosphate or tricresyl phosphate alone can improve the tribological behavior of TiO₂ coating/AISI 1045 steel, and (ii) triphenyl thiophosphate with the same percentage was more efficacious than tricresyl phosphate in reducing the friction coefficient and wear rate [86]. Ti-doped carbon coating was employed for improvement the tribological performance of Ti–6Al–4V alloy [87]. Ti-doped carbon coatings were deposited on

Ti–6Al–4V alloy by reactive dc-magnetron sputtering in Ar/CH₄ mixed gas. When Ar flow increases, the incorporation of Ti into films rises while the concentration of carbon decreases. The formed nanometric TiC crystals were more noticeable for coatings deposited with higher Ar flows. Hardness and elastic modulus of coatings were measured by nanoindentation. Hardness values were in the range of 8.8–15.9 GPa and elastic modulus of 53.4–113.7 GPa. Higher values for hardness and elastic modulus were obtained for films containing larger amount of TiC-phase. The presence of TiC crystals increased the coefficient of friction from 0.07 to 0.28. Tribological experiments were carried out by a pin-on-disk apparatus in air and in liquid. The coefficient of friction values ranged from 0.10 to 0.50 for tests in air [87]. Furthermore, nitridation can improve the tribological performance [88]. Studying the tribological behavior of amorphous carbon and graphite/Ti–6Al–4V couples in pin-on-disk apparatus in an ambient atmosphere, Sylvestre et al. [88] reported that (i) N₂–H₂ plasma nitriding at a low temperature (700°C) for 12 h made the surface hardness improve by a factor of 3, (ii) with nitriding of Ti–6Al–4V, the friction coefficient is marked by a very important increase during a short time, and (iii) with the pin in graphite, the nitriding decreases the friction and increases the adhesion on the disk [88].

Badita et al. [89] uniquely adopted nanostructured coatings to improve tribological characteristics for Ti–6Al–4V hip prostheses. Nanostructured coatings were prepared with titanium nitride TiN, chromium nitride CrN, and chromium oxide Cr₂O₃. It was concluded that (i) the friction is highest in tests with CrN and slightly lower for TiN, (ii) from the tribological point of view, a favorable coating material needs to exhibit an elastic modulus which is similar to that of the substrate material (which is related to mechanical compatibility as the present author indicates and proposed several sections in this second edition), and (iii) the wear rate and friction coefficient decreases in physiological serum for a Ti–6Al–4V + TiN/UHMWPE hip prosthesis [89].

References

- [1] Alexander RMcN. Introduction to biotribology: animal locomotion. *J Eng Tribol* 2006;220:649–56.
- [2] Suresh S. *Fatigue of materials*. Cambridge: Cambridge University Press; 1991.
- [3] Piattellei A, Piattelli M, Scarano A, Montesani L. Light and scanning electron microscopic report of four fractured implants. *Int J Oral Maxillofac Implants* 1998;13:561–4.
- [4] Guichet DL, Caputo AA, Choi H, Sorensen JA. Passivity of fit and marginal opening in screw- or cement-retained implant fixed partial denture designs. *Int J Oral Maxillofac Implants* 2000;15:239–46.
- [5] Kotake M, Wakabayashi N, Ai M, Yoneyama T, Hamanaka H. Fatigue resistance of titanium–nickel alloy cast clasps. *Int J Prosthodont* 1997;10:547–52.
- [6] Rodrigues RCS, Ribeiro RF, da GC, de Mattos M, Bezzon OL. Comparative study of circumferential clasp retention force for titanium and cobalt–chromium removable partial dentures. *J Prosthet Dent* 2002;88:290–6.

- [7] Lewis AJ. Fatigue of removable partial denture casting during service. *J Prosthet Dent* 1978;39:147–9.
- [8] Rohlmann A, Bergmann G, Graichen F, Mayer HM. Placing a bone graft more posteriorly may reduce the risk of pedicle screw breakage: analysis of an unexpected case of pedicle screw breakage. *J Biomech* 1998;31:763–7.
- [9] Garcia R, Gorin S. Failure of posterior titanium atlantoaxial cable fixation: case studies. *Spine J* 2003;3:166–70.
- [10] Long M, Rack HJ. Titanium alloys in total joint replacement: a materials science perspective. *Biomaterials* 1998;19:1621–39.
- [11] Duerig TW, Pelton AR, Stöckel D. The use of superelasticity in medicine. *Metall* 1996;50:569–74.
- [12] Vallittu PK, Kokkonen M. Deflection fatigue of cobalt–chromium, titanium and gold alloys cast denture clasp. *J Prosthet Dent* 1995;74:412–9.
- [13] Lin C-W, Ju C-P, Lin J-HC. A comparison of the fatigue behavior of cast Ti–7.5Mo with c.p. titanium, Ti–6Al–4V and Ti–13Nb–13Zr alloys. *Biomaterials* 2005;26:2899–907.
- [14] Keltjens HM, Mulder J, Kayser AF, Creugers NH. Fit of direct retainers in removable partial dentures after 8 years of use. *J Oral Rehabil* 1997;24:138–42.
- [15] Saito M, Notani K, Miura Y, Kawasaki T. Complications and failures in removable partial dentures: a clinical evaluation. *J Oral Rehabil* 2002;29:627–33.
- [16] Hogmann E, Behr M, Handel G. Frequency and costs of technical failures of clasp- and double crown-retained removable partial dentures. *Clin Oral Investig* 2002;6:104–8.
- [17] Carr AB, McGivney GP, Brown DT. McCracken's removable partial prosthodontics. 11th ed. St. Louis, MO: Elsevier; 2005. p. 79–115
- [18] Vallittu PK. Fatigue resistance and stress of wrought-steel wire clasps. *J Prosthet Dent* 1996;6:186–92.
- [19] Gapido CG, Kobayashi H, Mitakawa O, Kohno S. Fatigue resistance of cast occlusal rests using Co–Cr and Ag–Pd–Cu–Au alloys. *J Prosthet Dent* 2003;90:261–9.
- [20] Yuasa Y, Sato Y, Ohkawa S, Nagasawa T, Tsuru H. Finite element analysis of the relationship between clasp dimensions and flexibility. *J Dent Res* 1990;69:1664–8.
- [21] Sato Y, Yuasa Y, Akagawa Y, Ohkawa S. An investigation of preferable taper and thickness ratios for cast circumferential clasp arms using finite element analysis. *Int J Prosthodont* 1995;8:392–7.
- [22] Sato Y, Abe Y, Yuasa Y, Akagawa Y. Effect of friction coefficient on Akers clasp retention. *J Prosthet Dent* 1997;78:22–7.
- [23] Mahmoud A, Wakabayashi N, Takahashi H, Ohyama T. Deflection fatigue of Ti–6Al–7Nb, Co–Cr, and gold alloy cast clasps. *J Prosthet Dent* 2005;93:183–8.
- [24] Styles CM, Evans SL, Gregson PJ. Development of fatigue lifetime predictive test methods for hip implants: Part I. Test methodology. *Biomaterials* 1998;19:1057–65.
- [25] Zavanelli RA, Guilherme AS, Pessanha-Henriques GE, Antônio De Arruda Nóbilo M, Mesquita MF. Corrosion-fatigue of laser-repaired commercially pure titanium and Ti–6Al–4V alloy under different test environments. *J Oral Rehabil* 2004;31:1029–34.
- [26] Guilherme AS, Henriques GEP, Zavanelli RA, Mesquita MF. Surface roughness and fatigue performance of commercially pure titanium and Ti–6Al–4V alloy after different polishing protocols. *J Prosthet Dent* 2005;93:378–85.
- [27] Malinov S, Sha W. Modeling thermodynamics, kinetics, and phase transformation morphology while heat treating titanium alloys. *J Metals* 2005;67:42–5.

- [28] Akahori T, Niinomi M, Fukunaga K-I, Inagaki I. Biomedical [alpha/beta] titanium alloys. *Metall Mater Trans A* 2000;31A:1949–58.
- [29] Koahn DH, Ducheyne PH, Awerbuch J. Acoustic emission during fatigue of porous-coated Ti–6Al–4V implant alloy. *J Biomed Mater Res* 1992;26:19–38.
- [30] Wagner L, Gregory JK. Improve the fatigue life of titanium alloys. Part I. *Adv Mater Processes* 1994;146:35–6.
- [31] Wagner L, Gregory JK. Improve the fatigue life of titanium alloys. Part II. *Adv Mater Processes* 1994;146:50–3.
- [32] Li SJ, Niinomi M, Akahori T, Kasuga T, Yang R, Hao YL. Fatigue characteristics of bioactive glass-ceramic-coated Ti–29Nb–13Ta–4.6Zr for biomedical application. *Biomaterials* 2004;25:3369–78.
- [33] Polakowski NH, Ripling EJ. Strength and structures of engineering materials. Englewood Cliffs, NJ: Prentice-Hall; 1966. p. 516–7
- [34] Budinski K. Engineering materials—properties and selection. 2nd ed. Virginia: Prentice-Hall; 1983. p. 237.
- [35] Zivić F, Babić M, Grujović N, Mitrović. Tribometry of materials for bioengineering applications. *Tribol Ind* 2010;32:25–32.
- [36] Yu HY, Quan HX, Cai ZB, Gao SS, Zhu MH. Radical fretting behavior of cortical bone against titanium. *Tribol Lett* 2008;31:69–76.
- [37] Cai ZB, Zhang GA, Zhu YK, Shen MX, Wang LP, Zhu MH. Torsional fretting wear of a biomedical Ti6Al7Nb alloy for nitrogen ion implantation in bovine serum [Abstract only]. *Tribol Int* 2012; <http://dx.org/10.1016/j.triboint.2012.06.0009>.
- [38] Clemens V, Mo JL, Zhu MH, Shen MX, Zhou ZR. Research on the rotational fretting wear of Ti6Al4V alloy against silicon nitride. *J Eng Tribol* 2010;224:1181–7.
- [39] Banerjee R, Nag S, Stechschulte J, Fraser HL. Strengthening mechanisms in Ti–Nb–Zr–Ta and Ti–Mo–Zr–Fe orthopaedic alloys. *Biomaterials* 2004;25:3414–9.
- [40] Steinmann SG. Corrosion of surgical implants—in vivo and in vitro tests. In: Winter GD, Leray JL, de Groot K, editors. *Evaluation of biomaterials*. New York, NY: Wiley; 1980.
- [41] Seah KHW, Thampuran R, Teoh SH. The influence of pore morphology on corrosion. *Corros Sci*. 1998;40:547–56.
- [42] Rao S, Uchida T, Tateishi T, Okazaki T, Asao Y. Effect of Ti, Al and V ions on the relative growth rate of fibroblasts (L929) and osteoblasts (MC3T3-E1) cells. *J Biomed Mater Eng* 1996;6:79–86.
- [43] Walker PR, LeBlanc J, Sikorska M. Effects of aluminum and other cations on the structure of brain and liver chromatin. *Biochemistry* 1989;28:3911–5.
- [44] Kim K-H, Choi M-Y, Kishi T. Fracture analysis of cast pure Ti and Ti–6Al–4V alloy for dental use. *J Biomed Mater Eng* 1997;7:271–6.
- [45] Ivasishin OM, Markovsky PE. Enhancing the mechanical properties of titanium alloys with rapid heat treatment. *J Met* 1996;48:48–61.
- [46] Mante FK, Baran GR, Lucas B. Nanoindentation studies of titanium single crystals. *Biomaterials* 1999;20:1051–5.
- [47] Tanaka S, Takahashi Y, Tajima S, Shiratori N, Ito M. Relationship between heat treatment and properties for titanium implant material. *J Jpn Soc Oral Implantol* 2004;17:202–8.
- [48] Dumbleton JH. *Tribology series 3: tribology of natural and artificial joints*. New York, NY: Elsevier; 1981.

- [49] Harper LH, Dooris A, Paré PE. The fundamentals of biotribology and its application to spine arthroplasty. *SAS J* 2009;3:125–32.
- [50] Chromik RR, Strauss HW, Scharf TW. Materials phenomena revealed by *in situ* tribometry. *J Met* 2012;31:35–43.
- [51] Zwicker U, Breme J. Investigations of the friction behaviour of oxidized Ti–5% Al–2.5%Fe surface layers on implant material. *J Less-Common Met* 1994;100:371–5.
- [52] Stannard JG, Gau JM, Hanna MA. Comparative friction of orthodontic wires under dry and wet conditions. *Am J Orthod* 1986;89:485–91.
- [53] Kapila S, Angolkar PV, Duncanson MG, Nanda RS. Evaluation of friction between edgewise stainless steel brackets and orthodontic wires of four alloys. *Am J Orthod Dentofacial Orthop* 1990;98:117–26.
- [54] Angolkar PV, Kapila S, Duncanson MG, Nanda RS. Evaluation of friction between ceramic brackets and orthodontic wires of four alloys. *Am J Orthod Dentofacial Orthop* 1990;98:499–506.
- [55] Kusy RP, Whitley JQ, Prewitt MJ. Comparison of the frictional coefficients for selected archwire-bracket slot combinations in the dry and wet state. *Angle Orthod* 1991;61:293–301.
- [56] Prosski RR, Bagby MD, Erickson LC. Static frictional force and surface roughness of nickel–titanium arch wires. *Am J Orthod Dentofacial Orthop* 1991;100:341–8.
- [57] Oshida Y, Kotona TR, Farzin-Nia F, Rosenthal MR. Comparison of frictional forces between three grades of low friction “colors” TMA. In: Shrivastava S, editor. *Medical device materials*. Materials Park, Novelty, OH: ASM International; 2004. p. 455–8.
- [58] Thompson GJ, Puleo DA. Ti–6Al–4V ion solution inhibition of osteogenic cell phenotype as a function of differentiation time course *in vitro*. *Biomaterials* 1996;17:1949–54.
- [59] Bianco DP, Ducheyne P, Cuckler JM. Titanium serum and urine levels in rabbits with a titanium implant in the absence of wear. *Biomaterials* 1996;17:1937–42.
- [60] Davidson JA, Mishra AK. Surface modification issues for orthopaedic implant bearing surfaces. In: Sudarshan TS, editor. *Surface modification technologies*. Cambridge: The University Press [The Institute of Materials]; 1992. p. 1–14.
- [61] Lausmaa J, Roestlund T, McKellop H. Wear of ion-implanted pure titanium and Ti–6Al–4V alloy against UHMWPE. In: Sudarshan TS, editor. *Surface modification technologies*. Cambridge: The University Press [The Institute of Materials]; 1992. p. 139–54.
- [62] Bartolovic DJ. *In vitro* wear characterization of Ti–6Al–7Nb for dental prostheses against high-fusing porcelain. Indiana University Master Thesis; 2005.
- [63] Haynes DR, Boyle SJ, Rogers SD, Susan D, Howie DW, Barrie V-R. Variation in cytokines induced by particles from different prosthetic materials. *Clin Orthop* 1998;352:223–30.
- [64] Nakashima Y, Sun DH, Trindale MC, Trindale MCD, Chun LE, Song Y, et al. Induction of macrophage C–C chemokine expression by titanium alloy and bone cement particles. *J Bone Joint Surg Br* 1999;81:155–62.
- [65] Shanbhag AS, Jacobs JJ, Black J. Human monocyte response to particulate biomaterials generated *in vivo* and *in vitro*. *J Orthop Res* 1995;13:792–801.
- [66] Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Macrophage/particle interactions: effect of size, composition and surface area. *J Biomed Mater Res* 1994;28:81–90.
- [67] Howie DW, Rogers SD, McGee MA, Haynes DR. Biologic effects of cobalt chrome in cell and animal models. *Clin Orthop* 1996;329S:S217–32.

- [68] Maloney WJ, Smith RL, Castro F, Schurman DJ. Fibroblast response to metallic debris *in vitro*. Enzyme induction cell proliferation and toxicity. J Bone Joint Surg Am 1993;75:835–44.
- [69] Haynes DR, Rogers SD, Howie DW, Pearcy MJ, Barrie V-R. Drug inhibition of the macrophage response to metal wear particles *in vitro*. Clin Orthop 1996;323:316–26.
- [70] Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Effects of particles on fibroblast proliferation and bone resorption *in vitro*. Clin Orthop 1997;342:205–17.
- [71] Black J. Biological performance of materials: fundamental of biocompatibility. New York, NY: Marcel Dekker; 1992.
- [72] Catelas I, Petit A, Zukor DJ, Marchand R, Yahia LH, Huk OL. Induction of macrophage apoptosis by ceramic and polyethylene particles *in vitro*. Biomaterials 1999;20:625–30.
- [73] Kubo T, Sawada K, Hirakawa K, Shimizu C, Takamatsu T, Hirasawa Y. Histiocyte reaction in rabbits femurs to UHMWPE, metal, and ceramic particles in different sizes. J Biomed Mater Res 1999;45:363–9.
- [74] Catelas I, Huk OL, Petit A, Zukor DJ, Marchand R, Yahia LH. Flow cytometric analysis of macrophage response to ceramic and polyethylene particles: effects of size, concentration, and composition. J Biomed Mater Res 1998;41:600–7.
- [75] Yoon TR, Rowe SM, Jung ST, Seon KJ, Maloney WJ. Osteolysis in association with a total hip arthroplasty with ceramic bearing surfaces. J Bone Joint Surg Am 1998;80:1459–68.
- [76] Stea S, Visentin M, Granchi D, Cenni E, Ciapetti G, Sudanese A, et al. Apoptosis in peri-implant tissue. Biomaterials 2000;21:1393–8.
- [77] Chiba J, Rubash H, Kim KJ, Iwaki Y. The characterization of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. Clin Orthop Relat Res 1994;300:304–12.
- [78] Perry M, Murtuza FY, Ponsford FM, Elson CJ, Atkins RM, Learmonth D. Properties of tissue from around cemented joint implants with erosive and/or linear osteolysis. Arthroplasty 1997;12:670–6.
- [79] Ingham E, Fisher J. The role of macrophages in osteolysis of total hip joint replacement. Biomaterials 2005;26:1271–86.
- [80] Luo Y, Ge S, Liu H, Jin Z. Microstructure analysis and wear behavior of titanium cement femoral head with hard TiC layer. J Biomech 2009;42:2708–11.
- [81] El-Tayeb NSM, Yap TC, Brevern PV. On the tribo-cryogenic characteristics of titanium alloys. J Eng Tribol 2010;224:395–409.
- [82] Majumdar P, Singh SB, Chakraborty M. Wear response of heat-treated Ti–13Zr–3Nb alloy in dry condition and simulated body fluid. Wear 2008;264:1015–25.
- [83] Gülleryüz H, Çimenoglu H. Effect of thermal oxidation on corrosion and corrosion-wear behaviour of a Ti–6Al–4V alloy. Biomaterials 2004;25:3325–33.
- [84] Miyakawa O, Okawa S, Kobayashi M. Abrading increases oxygen and hardness of titanium surface. Dent Mater J 2006;25:13–9.
- [85] Diaz C, Lutz J, Mädl S, Garcia JA, Mantinez R, Rodriguez RJ. Improved bio-tribology of biomedical alloys by ion implantation techniques. Beam Interact Mater Atoms 2009;267:1630–3.
- [86] Jiang SY, Xie HJ. Tribological behavior of plasma-spray TiO₂ coating against metallic bearing materials under oil lubrication. J Eng Tribol 2011;225:128–38.
- [87] Júnior ES, Júnior SSC, Soares GA, Delplancke-Ogletree MP. Mechanical and tribological properties of Ti-containing carbon nanocomposite coatings deposited on TiAlV alloys. Mat Res 2010;13:113–24.

-
- [88] Sylvestre M, Zaidi H, Riviè JP, Eyidi D, Doyen F. Amelioration of the tribological behavior of carbon/Ti–6Al–4V and graphite/Ti–6Al–4V couples by plasma nitriding of the titanium alloy. *J Eng Tribol* 2010;224:979–88.
 - [89] Gheorghe GI, Bădiță LL. Tribological Improvement and characterization of hip prostheses with nanostructured surfaces using advanced microtechnologies and atomic force microscopy. *Digest J Nanomater and Biostructures* 2012;7:529–35.

This page intentionally left blank

6 Biological Reactions

6.1 Introduction

It is important to know the behaviors of titanium materials that are exposed to natural/biological environment. This chapter will discuss biological reactions, and reactions in biomechanical environment in general, with a particular emphasis on discrete stress field under strain continuum situation since this concept should be essential for designing and material selection for dental and orthopedic implants.

6.2 Toxicity

Toxicity can be measured by the effects on the target (organism, organ, or tissue). Because individuals typically have different levels of response to the same dose of a toxin, a population-level measure of toxicity is often used which relates the probability of an outcome for a given individual in a population. One such measure is the LD₅₀ (LD stands for Lethal Dose), which is a concentration measure for a toxin at which 50% of the members of an exposed population die from exposure [1]. When such data does not exist, estimates are made by comparison to known similar toxic things or to similar exposures in similar organisms. Then the safety factors must be built in to protect against the uncertainties of such comparisons, in order to improve protection against these unknowns. Toxicity can refer to the effect on a whole organism (such as a human, a bacterium, or a plant), or to a substructure (such as the liver, kidney, and spleen). In the science of toxicology, the subject of such study is the effect of an external substance or condition and its deleterious effects on living things: organisms, organ systems, individual organs, tissues, cells, and subcellular units. Toxicity of a substance can be affected by many different factors, such as the route of administration, the time of exposure, the number of exposures, physical form of the toxin (solid, liquid, gaseous), the genetic makeup of an individual, an individual's overall health, and many others.

There are generally three types of toxic entities: chemical, biological, and physical.

(1) *Chemicals* include both inorganic substances, such as lead, hydrofluoric acid, and chlorine gas, as well as organic compounds such as ethyl alcohol, most medications, and poisons from living things. Chemicals (which can be toxic) should include corrosion product such as oxides, chlorides, or sulfides as well as

dissolved metallic ions through anodic reaction. The toxicity is related to primary biodegradation products (simple and complex cations and anions), particularly those of higher atomic weight metals. Factors to be considered include (i) the amount dissolved by biodegradation per time unit, (ii) the amount of material removed by metabolic activity in the same time unit, and (iii) quantities of solid particles and ions deposited in the tissue and any associated transfers to the systemic system. Hence, the extent of toxicity is indirectly related to corrosion rate [2–5]. An *in vivo* corrosion experiment can always be followed up by a tissue examination. This type of tissue reaction is observed for both corrosion-resistant materials (Mo-containing stainless steel and Co–Cr–Mo alloys) and for the strongly corroding metals Fe, Mo, and Al. It must be assumed that the unwanted corrosion product itself is the determining factor. Elements like Fe, Mo, and Al (as nontoxic metals) do not trigger an extreme tissue reaction despite high corrosion rates (about 300 times higher than that of stainless steel). On the other hand, the very low corrosion rates of stainless steel and Co–Cr alloys, comparable to that of Ti, Nb, and Zr, release sufficient quantities of the highly toxic elements nickel and cobalt, to trigger a noticeable tissue reaction. It should be mentioned at this point that no limiting concentration is commonly admitted for an allergic reaction. Gold and silver are also to be found in this middle group, as these noble metals can also corrode in living tissue. As demonstrated above, a low corrosion rate alone is not sufficient to guarantee compatibility, nor is the elemental dose the only determining factor. It would appear that the intrinsic toxicity of the element and its ability to bind to macromolecules are equally important. Chemical data for Ti, Zr, Nb, and Ta show that organic complexes of this type are unlikely, and it is also known that organometallic compounds of these elements, as far as they exist, are unstable [6].

There are certain types of elements which are essential for living organisms and types of elements are different between kinds of living substances. For plants, there are macronutrients including N, P, S, Ca, Mg, and Fe, and micronutrients such as Mn, Zn, Cu, Mo, B, and Cl (www.soils.wisc.edu). On the other hand, essential trace elements for living organisms (particularly the higher animals) include Fe, F, Si, Zn, Sr, Pb, Mn, Cu, Sn, Se, I, Mo, Ni, B, Cr, As, Co, and V. Among these elements, the following nine elements are considered as the most important bioelements, since they are able to exist as a constituting element for metalloproteins, metalloenzymes, or even vitamins: Fe, Zn, Mn, Cu, Se, Mo, Ni, Co, and V [7,8].

Despite reports associating tissue necrosis with implant failure, the degree to which processes, such as metal toxicity, negatively impact implant performance is unknown. Hallab et al. [9] evaluated representative human perimplant cells (i.e., osteoblasts, fibroblasts, and lymphocytes) when challenged by Al^{+3} , Co^{+2} , Cr^{+3} , Fe^{+3} , Mo^{+5} , Ni^{+2} , and V^{+3} chloride solutions (and Na^{+2} as a control) over a wide range of concentrations (0.01–10.0 mM). It was reported that (i) differential effects were found to be less a function of the cell type than of the composition and concentration of metal challenge, (ii) no preferential immunosuppression was demonstrated, and (iii) soluble Co released from Co–Cr alloy and V released from Ti–6Al–4V alloy could be implicated as the most likely to mediate cell toxicity in the periprosthetic milieu [9].

Maurer et al. [10], using diluted concentration of vanadate and titanium tetrachloride as salts, investigated the cellular uptake of titanium and vanadium. It was found that (i) titanium was not observed to be toxic to the cells, but (ii) vanadium was toxic at levels greater than 10 $\mu\text{g/mL}$. The percentage of cellular association of titanium was shown to be about 10 times that of vanadium. The percentage of cellular association of either element was greater from fretting corrosion than from the addition of salts. It was also mentioned that (i) the presence of vanadium did not affect the cellular uptake of titanium, but (ii) the presence of titanium decreased the cell association of vanadium [10].

Corrosion resistance is one of the most important properties which can determine the biocompatibility of metallic biomaterials. The high corrosion resistance of metallic materials is attributed to a passive film on their surfaces. However, the passive film on these metals may be continuously damaged by wear when these materials are used as bone plates and screws, artificial joints, or dental restorations. The wear on metallic biomaterials can generate debris and accelerate metal ion release. Powders of Co–Cr–Mo alloy were produced by grinding larger particles for 8 h in water, serum, or joint fluid, and were administered in low doses (0.05–0.5 mg/mL) for 1–6 days to human dermal fibroblasts *in vitro*. Particles were ground in a biological fluid in order to simulate conditions in an artificial hip joint. It was found that (i) such particles adhered to, or were phagocytosed, by the cells far less than those ground in water, and (ii) the toxicity of the alloy was linked with a failure of test cells to grow as quickly as the controls—particles ground in water were the most toxic [11].

(2) *Biological* toxicity can be more complicated to measure. In a host with an intact immune system, the inherent toxicity of the organism is balanced by the host's ability to fight back; the effective toxicity is then a combination of both parts of the relationship. A similar situation is also present with other types of toxic agents. In particular, toxicity of cancer-causing agents is problematic, since for many such substances it is not certain if there is a minimal effective dose or whether the risk is just too small to see. Here, too, the possibility exists that a single cell transformed into a cancer cell is all it takes to develop the full effect. Yang et al. [12] demonstrated an increase in levels of elemental Ti in the blood and lung of rats with a Ti alloy implant. Rats were implanted with Ti alloy disks for 4 weeks. The levels of elemental Ti in the blood and lung were especially increased compared with other tissues. The Ti alloy implant enhanced lung injury related to endotoxin from gram-negative bacteria (lipopolysaccharide, LPS), which was characterized by lung edema and other histological changes such as recruitment of neutrophils, interstitial edema, and alveolar hemorrhage in the lung. In the presence of endotoxin, an increase of nitrite production was shown in the plasma and bronchoalveolar lavage fluid of rats implanted with a Ti alloy. Moreover, the Ti alloy implant further enhanced the induction of inducible nitric oxide (NO) synthase (iNOS) protein expression induced by LPS in the lung. These endotoxin-related responses in the presence or absence of the Ti alloy implant could be inhibited by aminoguanidine (an iNOS inhibitor). It was first indicated that circulating Ti released from Ti alloy implants had an ability to affect pulmonary iNOS protein expression, and enhance the pathogenesis of acute lung injury during endotoxemia [12].

(3) *Physically* toxic entities include things not usually thought of as such by the lay person: direct blows, concussion, sound and vibration, heat and cold, nonionizing electromagnetic radiation such as infrared and visible light, ionizing nonparticulate radiation, such as X-rays and gamma rays, and particulate radiation, such as alpha rays, beta rays, and cosmic rays (<http://en.wikipedia.org/wiki/Toxicity>).

Besides these, particulate macrophages should be included here; even species per se are not toxic, but because of size, they will exhibit physical toxicity. Particulate wear-debris is detected in histocyte/macrophages of granulomatous tissues adjacent to loose joint prostheses. Such cell–particle interactions have been simulated *in vitro* by challenging macrophages with particles dosed according to weight percent, volume percent, and number of particles. Each of these dosage methods has inherent shortcomings due to varying size and density of challenging particles of different compositions. In studies done by Shanbhag et al. [13], P388D1 macrophages with titania (TiO₂) and polystyrene particles (< 2 μm), with dosage based on the ratio of the cells, were challenged. The effect of size and composition on the bone reabsorbing activity and fibroblast proliferation was studied. It was reported that (i) macrophage response to particulate debris appears to be dependent on particle size, composition, and dose as given by surface area ratio, and (ii) macrophages stimulated by wear particles are expected to synthesize numerous factors affecting events in the bone-implant interface [13].

Recently, Takeda et al. [14] discussed the health effects of nanomaterials on the next generation. When discussing the health effects of nanomaterials, one cannot disregard the research on the health effects of airborne particles which could be any type of nanosized biomaterial (including fine powder of TiO₂). The results not only of animal experiments but also of many epidemiologic surveys and volunteer intervention experiments in humans have reported on the health effects of particles. Although the health effects of particle sizes below 10 μm were investigated in the initial studies, recently even smaller particles have come to be regarded as questionable and research on the health effects of minute particulate matter below 2.5 μm has been done. The health effects of various types of intentionally produced nanomaterials such as carbon black, carbon nanotube (which is recently becoming very popular material in the advanced tissue engineering field), fullerene, and titanium dioxide were examined on their influence on the next generation. Regardless of dosage and administration method, such as inhalation, endotracheal administration, nasal drip, and subcutaneous administration, once nanomaterials enter the bloodstream of a pregnant mother mouse, they move to the offspring and have effects on them. The effects may appear as various symptoms in the process of growth after birth, and can sometimes lead to the onset and aggravation of serious diseases [14].

6.3 Cytocompatibility (Toxicity to Cells)

Over the years, many metal and polymer implants have been developed for internal fracture fixation. However, there are some problems associated with their application, such as implant loosening or infection. Cytotoxicity of soluble and particulate

Ti, V, and Ni by biochemical functional analysis and by microscopic morphology with elemental analysis *in vitro* using human neutrophils as probes and *in vivo* in animals was compared. It was concluded that (i) the biochemical analysis of lactate dehydrogenase (LDH), superoxide anion, inflammatory mediator TNF- α , and scanning electron microscopy (SEM) showed that Ni in solution destroys the cell membranes of neutrophils, whereas Ti and V in solution stimulate neutrophils and increase the quantity of released superoxide anions, (ii) fine Ti particles (1–3 μm), which are smaller than neutrophils (about 5 μm), were phagocytized by the cells, and the results were similar *in vivo*, and (iii) these results showed that the cytotoxic effect of Ti particles is size dependent, and that they must be smaller than that of cells [15].

Harris et al. [16] studied the morphology and adhesion of both fibroblasts and osteoblasts to manufacture commercially pure, medical implant—quality anodized titanium surfaces, and five modified titanium surfaces, and examined their relative cytocompatibility to assess which modified surface could potentially be used *in vivo*. It was reported that (i) small variations were observed both qualitatively and quantitatively in the spreading and adhesion of fibroblasts and osteoblasts to the studied surfaces, but (ii) noticeable fibroblast and osteoblast spreading and adhesion were found on the anodized surfaces, and (iii) coating medical implant—quality anodized titanium surfaces could probably improve soft tissue adhesion and/or osseointegration of bone *in vivo* [16].

The cytotoxicity and mutagenicity of metal salts were systematically evaluated by Yamamoto et al. [17,18]. Metal ions released from the wear-debris of Ti alloys [19] and the cytotoxicity of ceramic particles (mainly metal oxides) [20] were investigated, and it was confirmed that active oxygen species generated by macrophages phagocytosing high-density polyethylene particles induced metal ion release from Ti [21].

Manceur et al. [22] reported on the biocompatibility of NiTi single crystals, since certain orientations of single crystals present several advantages over the polycrystalline form in terms of maximal strain, fatigue resistance, and temperature range of superelasticity (which is one of two uniquenesses associated with NiTi material; the other one is SME—shape memory effect). The *in vitro* biocompatibility evaluation of 50.8 wt%Ni–Ti single crystals in the orientation $\langle 001 \rangle$ was conducted after four different heat treatments in a helium atmosphere followed by mechanical polishing. The study was performed on the material extracts after immersion of the specimens in cell culture medium (DMEM) for 7 days at 37°C. Cytotoxicity studies were performed on L929 mouse fibroblasts using the MTT assay. The J774 macrophages were used to assess the potential inflammatory effect of the extracts by IL1- β and TNF- α dosage (sandwich ELISA method). It was found that (i) exposure of L929 to material extracts did not affect cell viability, and (ii) IL1- β and TNF- α secretion were not stimulated after incubation with NiTi extracts compared to the negative controls, concluding that TiNi single crystals did not trigger a cytotoxic reaction [22].

Titanium alloys have been proven to behave poorly in friction due to detection of wear particles in tissues and organs associated with titanium implants. Bordji et al. [23] investigated three surface treatments in order to improve the wear

resistance and the hardness of Ti–6Al–4V and Ti–5Al–2.5Fe: (1) glow discharge nitrogen implantation ($10\text{--}17\text{ atoms/cm}^2$), (2) plasma nitriding by plasma diffusion treatment (PDT), and (3) deposition of TiN layer by plasma-assisted chemical vapor deposition (PACVD) additionally to PDT. A cell culture model using human cells was chosen to study the effect of such treatments on the cytocompatibility of these materials. The results showed that (i) Ti–5Al–2.5Fe alloy was as cytocompatible as the Ti–6Al–4V alloy, and the same surface treatment led to identical biological consequences on both alloys, (ii) nitrogen implantation did not at all modify the cellular behavior observed on untreated samples, and (iii) after the two nitriding treatments, cell proliferation and viability appeared to be significantly reduced, and the SEM study revealed somewhat irregular surface states, but (iv) osteoblast phenotype expression and protein synthesis capacity were not affected. Hence, it was concluded that plasma diffusion nitriding treatment and TiN deposition by chemical vapor process may be an interesting alternative to the physical vapor deposition technique [23]. Wever et al. [24] carried out a dilution minimal essential medium extract cytotoxicity test, a guinea pig sensitization test and two genotoxicity (*Salmonella* reverse mutation and the chromosomal aberration) tests on NiTi. It was reported that the NiTi alloy showed no cytotoxic, allergic, or genotoxic activity similar to the clinical reference control material AISI 316 stainless steel.

With the prolonged use of NiTi material in a human body, deterioration of the corrosion resistance of the materials becomes a critical issue because of the increasing possibility of deleterious ions released from the substrate to living tissues. It was proven that a certain surface modifications, such as nitrogen, acetylene, and oxygen plasma immersion ion implantation (PIII or PI^3), can improve the corrosion resistance and mechanical properties of the materials. With this modification, it was reported that (i) the release of nickel is drastically reduced as compared with the untreated control, and (ii) the *in vitro* tests show that the plasma-treated surfaces are well tolerated by osteoblasts [25,26].

Although Ti–Ni alloy has been increasingly applied to medical and dental devices such as coronary stents and orthodontic wires, the alloy contains nickel, which is known to cause cytotoxicity, metal allergy, and carcinogenicity. The corrosion resistance of Ti–Ni alloy was studied by electrolytic treatment in lactic acid, water, and glycerol [27]. It was found that, with the electrolytic treatment, nickel concentration in the surface oxide layer decreased, and the thickness of the surface oxide layer increased.

A number of ternary NiTi–X alloys have been introduced with the aim of improving the fatigue properties and decreasing the thermal hysteresis range; well-known ternary alloying elements are Cu and Fe [10,12,28]. Particularly, Cu has been shown to dissolve in the B2 (austenitic) phase in concentrations up to 30 at.%. However, NiTi–Cu solid solutions containing more than 10 at.% are characterized by poor formability, so that alloys of technical interest usually contain Cu in the range from 5 to 10 at.%. NiTi (57.6 wt%Ni, 42.4 wt%Ti) and NiTiCu (50.7 wt%Ni, 42.4 wt%Ti, 6.9 wt%Cu) were evaluated by the Tada method [28]. It was concluded that (i) a significant difference in the *in vivo* biocompatibility between the binary and the ternary alloys was shown and (ii) the presence of the binary alloy

lead to few morphological changes and a slight reduction of dehydrogenase activity of epithelial cell cultures, whereas the effect of the ternary alloy appears to be more pronounced, obviously due to the releasing of copper ions [29].

Newly developed β -type titanium alloys, Ti–29Nb–13Ta–4.6Zr, CpTi, and Ti–6Al–4V were evaluated in terms of cytotoxicity [30]. Each plate specimen was put on zirconia (ZrO_2) balls in a vessel and in an autoclave. The vessel with 10 mL Eagle's culture solution at a temperature of 310 K was rotated with a speed of 240 rpm, and extraction periods were 7 and 14 days. As-extracted solution and filtrated extract solution using a 0.22 μm membrane filter were prepared. In the as-extracted solution and filtrated extracted solution, the survival rate of L929 cells derived from mice was evaluated using the NR [31] and MTT [32] methods. The exposure period of L929 cells to extract the solutions was 2 days. The MTT method is a method for evaluating cell respiration by the mitochondria, while the NR method is a method for evaluating the ratio of sound cells of which cell membranes have no lesion by the amount of Neutral Red (NR) pigment. The survival rate of L929 cells indicates the cytotoxicity level of the extracts, and it was also reported that the new alloy is equivalent to that of CpTi and Ti–6Al–4V [30].

Spriano et al. [33] treated Ti–6Al–7Nb as prosthetic implant material by various methods: surfaces were (1) mechanically polished with SiC paper, (2) passivated in 35 wt% HNO_3 for 30 min, (3) treated in alkali 5 M NaOH at 60°C for 24 h, (4) heated at 600°C for 1 h in air, and (5) heated at 600°C for 1 h in a vacuum. These treated surfaces were characterized in order to evaluate their surface properties and cell interaction, in order to assess whether the treatments were effective in obtaining a surface presenting at the same time bone-like apatite induction ability and low metal ion release. Wettability was examined by surface contact angle measurements. The untreated surface showed 55°, which was the highest value of surface contact angle, indicating that the untreated surface is not at active stage. On SiC-polished surface, it was 50°, followed by very low values of contact angle; the in-air oxidized surface exhibits almost 0° of contact angle, indicating very high wettability. It was also reported that such an active surface was covered with a film of a composition close to standard Ca/P ratio bone-like apatite after the surfaces were immersed in simulated body fluid (SBF) for 30 days [33].

Hou et al. [34] used the rat oral implant model to assess histological changes in the mechanical environment surrounding loaded and unloaded dental implants. The maxillary left first molar from rats was extracted, and the site was allowed to heal for 1 month. A titanium mini-screw implant was then placed into the site and allowed to heal for 21 days. The mandibular left first molars in one group of rats were extracted to create an unloaded condition. In a second group of rats, the mandibular left first molars were left in occlusion with the opposing screw head to simulate loading. Radiographs were taken on the day of placement and at 7 days, 14 days, and 21 days after postimplantation and were used to estimate the bone-implant contact (BIC) ratio. It was reported that (i) areas of high shear stress adjacent to the helical threads of loaded implants were associated with osteocalcin localization and bone formation but only minimal localization of matrix metalloproteinase 13, and (ii) bone adjacent to unloaded implants showed fibrous tissue

and extensive matrix metalloproteinase 13 localization surrounding the apical two-thirds of each implant [34].

Antibacterial effect and cytocompatibility of a nanostructured TiO₂ (titania) film containing Cl on CpTi surface were investigated [35]. The nanostructured TiO₂ was prepared by anodization with hydrofluoric acid, followed by secondary anodization with NaCl solution of different concentrations (0.4 M, 1 M, 2 M). The antibacterial effect was evaluated by film adhesion method and cytocompatibility was tested by the viability of MG-63 cells in an MTT assay. It was found that (i) the contact angle (as a function of surface wettability) showed anodized titanium as a hydrophilic nature and (ii) TiO₂ nanostructured film anodized in 1 M NaCl exhibited the best antibacterial effect and cell cytocompatibility [35]. The titanium dioxide layer is composed mainly of anatase and rutile, as described in Chapter 4. This layer is prone to break (mainly due to its brittle ceramic nature), releasing particles to the milieu. Based on previous finding that commercial anatase TiO₂ was deposited in organs with macrophagic activity, transported in the blood by phagocytic mononuclear cells, and induced an increase in the production of reactive oxygen species, Olmedo et al. [36] further evaluated the effects of rutile TiO₂, using male Wistar rats injected with a suspension of rutile TiO₂ powder. It was reported that (i) titanium was found in phagocytic mononuclear cells, serum, and in the parenchyma of all the organs tested, (ii) although rutile TiO₂ provoked an augmentation of reactive oxygen species, it failed to induce damage to membrane lipids, possibly due to an adaptive response, and (iii) rutile TiO₂ is less bioactive than anatase TiO₂ [36].

Normally, measuring the surface contact angle is performed by placing one liquid droplet onto the target substrate, followed by measuring height (h) of the droplet and length (d) of the droplet after wetting. Using the sphere approximation, the contact angle (θ) can be obtained by the formula $\theta = 2 \tan^{-1}(2h/d)$. And it is the common practice to measure the advancing angle instead of the receding angle which is much lower since the wetting front is traveling on an already-wet area. If the used liquid does not show any corrosiveness against the substrate surface material, the contact angle normally spreads; hence, the contact angle (θ) can be partial-differentiated with respect to time (t) as the formula $\delta\theta/\delta t = [-4h(\delta d/\delta t) + 4d(\delta h/\delta t)]/(d^2 + 4h^2)$.

In terms of wettability, hydrophilicity has been gaining increasing interest as a factor that might influence the osseointegration of dental implants. Rupp et al. [37], using nine screw-type implant systems from eight manufacturers, measured dynamic water contact angles using tensiometry. Wettability was quantified by first advancing contact angles. It was concluded that (i) the first advancing mean contact angles of all implants ranged from 0° to 138°, demonstrating statistically significant differences among implant systems and (ii) because of kinetic hysteresis, initially hydrophobic implants became to be hydrophilicity during following immersion loops.

6.4 Allergic Reaction

Allergy is the opposite of acquired immune deficiency syndrome (AIDS). Allergy symptoms are the result of too much immunity. The immune system

produces antibodies to fight infections. If one has AIDS, he/she has too little immunity to defend him/herself against getting sick. AIDS is too little immunity, and allergy is too much. Metal sensitivity is thought to be a very important factor in the overall biocompatibility of implants. Although titanium has not been found to show sensitivity, other materials such as nickel from stainless steel, other high-nickel alloys such as NiTi, and cobalt from cobalt-based alloys have been shown to be sensitizers in skin dermatitis and might, therefore, show an allergic response upon implantation [38]. Allergic contact dermatitis to metals is a common skin disease in many countries of the world. Ni allergy is most frequent, and the prevalence is reported to be 10% in females and 1% in males [39]. The incidence of Ni allergy has increased especially in the young female generation, where the cause is probably due to the increased habit of ear piercing in recent years [40,41]. Cr is another well-known metal allergen. Especially in men, occupational chromium dermatitis occurs among cement workers, Cr platters, and workers dealing with leather tanning [42].

Ti is considered as a nonsensitizing or less sensitizing metal, and the application of Ti materials is increasing rapidly in a variety of products such as eyeglass rims, wrist watches, eyeglass frames, and dental and medical devices and equipment. However, there are some reports of contact dermatitis due to Ti [43,44]. Titanium allergy is barely recognized in mainstream medicine—yet it was reported that as many as 1 in 10 people can be affected by it. For those afflicted with titanium allergy, the symptoms can be multiple and bewildering. These can range from simple skin rashes to muscle pain and fatigue. From foodstuff to medicine, titanium is now an everyday metal. Several brands of candy, such as Skittles and M&M, have titanium dioxide in the coating—often described by its E-number: E171. Some brands of toothpaste and cold medicine contain titanium particles, as discussed in Chapter 4. Like all metals, titanium releases particles through normal corrosion. These metals become ions in the body and then bind to body proteins. In those who react, the body will try to attack this structure. This starts a chain reaction which can lead to many symptoms including chronic fatigue syndrome (CFS) or, in the most severe cases, multiple sclerosis (MS). The MELISA[®] test is the only scientifically proven test that can diagnose titanium allergy and measure its severity. Those who test positive should avoid exposure or remove the titanium from their body to stop the internal reaction. This can be simple, like changing one's brand of toothpaste. Or it may be more complex, such as replacing titanium implants (<http://www.melisa.org>).

Identification of the causative chemical of contact dermatitis, comparison of the sensitization potency of chemicals, and the finding of cross-reactivity among these chemicals are important to develop a safe material for the metal-sensitized patients. For this purpose, reproducible animal models are useful. Cr sensitization is easily induced in animals by using potassium dichromate, which is recognized as a strong sensitizer [45–49]. Although the sensitization rate to Ni in humans is the highest among various allergens, the sensitization potential of Ni salts was reported to be weak to mild in the animal studies [45,46,50–53]. On the other hand, there is little knowledge about the sensitization potential of zirconium and titanium salts by

animal assays using these salts. Ikarashi et al. [54] evaluated contact sensitization capacity of four metal salts, nickel sulfate (NiSO_4), potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$), titanium chloride (TiCl_4), and zirconium chloride (ZrCl_4), using guinea pigs and mice. In the guinea pig sensitization tests, an injection concentration to 1% for all chemicals was set up, and the challenge concentration was changed. Guinea pigs were sensitized with NiSO_4 , $\text{K}_2\text{Cr}_2\text{O}_7$, and TiCl_4 . It was found that (i) among the test metal salts, $\text{K}_2\text{Cr}_2\text{O}_7$ showed the highest sensitization rate and strongest skin reactions, (ii) ZrCl_4 did not cause any sensitization responses under our experimental conditions, (iii) minimal challenge concentration to cause a skin response was <0.25% for $\text{K}_2\text{Cr}_2\text{O}_7$, 0.5% for NiSO_4 , 2% for TiCl_4 , and (iv) in the sensitive mouse lymph node assay, TiCl_4 as well as ZrCl_4 caused mild lymph node responses but was classified as a nonsensitizer. Based on these findings, it was concluded that the order of sensitization potential was $\text{K}_2\text{Cr}_2\text{O}_7 > \text{NiSO}_4 > \text{TiCl}_4 > \text{ZrCl}_4$ [54].

Titanium brackets are used in orthodontic patients with an allergy to nickel and other specific substances. Harzer et al. [55] studied the corrosive properties of fluoride-containing toothpastes with different pH values on titanium brackets. Molar bands were placed on 18 orthodontic patients. In these same patients, titanium brackets were bonded on the left quadrants and stainless steel brackets on the right quadrants of the upper and lower arches. Fifteen patients used Gel Kam containing soluble tin fluoride (pH 3.2), whereas three used fluoride-free toothpaste. The brackets were removed for evaluation by light microscopy and scanning microscopy 5.5–7.0 months and 7.5–17 months after bonding. It was observed that (i) the matte gray color of titanium brackets dominating over the silver gleam of the steel brackets was noticed, (ii) the plaque accumulation on titanium brackets was high, and (iii) pitting corrosion and crevices were observed in only three of the 165 brackets tested. It was concluded that the *in vivo* study confirms the results of *in vitro* studies, but the changes are so minor that titanium brackets can safely be used for up to 18 months [55].

Although no cytotoxic effect caused by NiTi alloy has been reported [56], information concerning the biological side effects of Ni is available in literature [57–60]. Ni is capable of eliciting toxic and allergic responses [57]. Ni can produce more allergic reactions than all other metal elements [58]. The *in vivo* study, NiTi alloys show cytotoxic reactions [59]. Cases also show the conversion of Ni-nonsensitive subjects into Ni-sensitive subjects following the use of NiTi wires [60].

It is well documented that some metals are known to produce inflammatory responses (e.g., Cr, Co, Cu, Ni, Pd, Ti, Zr, and their based alloys) *in vitro* [61–63] and allergic reactions (e.g., Cr, Co, Ni, Ti, and NiTi) *in vivo* [64,65]. Several studies highlight that elements can diffuse from appliances and accumulate in tissues [66,67]. Ti–6Al–4V is the most frequently employed as an orthopedic implant material as well as device. However, it was reported that Al is an element involved in severe neurological (e.g., Alzheimer) disease [68] and metabolic-bone disease (e.g., osteomalacia) [69]. Al accumulated in bone is only a temporal soft tissue deprivation [70]. Bone remodeling will produce further Al release, even after the appliances no longer leach out Al, perpetrating the dangerous side effect of this

element [68,69]. Zaffe et al. [70] studied CpTi plates, Ti–6Al–4V screws, and surrounding tissues to evaluate the release and accumulation of ions. Optical microscopy, SEM and X-ray microanalysis were carried out to evaluate the plates and screws removed from patients presenting inflammation and biopsies. It was reported that (i) ions released from metallic appliances or leaching from granules toward soft tissues was observed, (ii) an accumulation of Al but not Ti was found in soft tissues, and (iii) a peculiar accumulation of Al in the dense lamella of newly formed bone was recorded, indicating that biological perturbations may be related to Al release from the tested biomaterials [70].

6.5 Metabolism

Most attempts to determine the concentration of titanium in animals and plant tissues have met with little success because of the very low levels involved [71]. In humans, the highest levels of titanium appear to be associated with the spleen and adrenals, at around 10 $\mu\text{g}/100\text{ g}$ with much lower amounts in the liver (3 μg) and kidneys (1.5 μg). It was demonstrated that there is increased titanium content in the lungs with increasing age in humans, but there was little evidence of accumulation in other tissues [72]. Very little exists concerning the metabolism of titanium and indeed there is some confusion over this subject. Generally, it appears there is little absorption of titanium in the gastrointestinal system, although the little that is absorbed appears to be stored in the heart, lungs, spleen, and kidneys of experimental animals [73].

It has been shown that titanium oxide (TiO_2) is transported in blood by phagocytic monocytes and deposited in organs such as liver, spleen, and lung 6 months after intraperitoneal injection [74]. Furthermore, it is well known that exposure to metal traces alters the cellular redox status. Rats were intraperitoneally injected with 1.60 g/100 g body weight of TiO_2 in saline solution. Organs (liver, spleen, and lung) were processed for histological evaluation. Reactive oxygen species in alveolar macrophages obtained by bronchoalveolar lavage were evaluated using the nitroblue tetrazolium test and quantitative evaluation by digital image analysis. It was found that (i) the histological analysis of organs revealed the presence of titanium in the parenchyma of these organs with no associated tissue damage, and (ii) although in lung alveolar macrophages TiO_2 induced a significant rise in reactive oxygen species generation, it failed to cause tissue alteration [75].

Schlegel et al. [76] evaluated the Ti level within the mucoperiosteal flaps covering submerged Ti implants. It was assumed that implant-covering flap was never absolutely immobile, and the existing small movement may have led to an eraser-like effect which impregnated the tissue continuously with titanium. Since Ti transfer to the mucoperiosteal flap during insertion is only a minor possibility due to the standardized surgical technique, the eraser-like effect may be the only remaining explanation. The investigated material included 38 biopsies taken after 2.4–18 months after implant insertion. Any influence of the implantation trauma

itself was excluded due to the evident time delay between implantation and taking the biopsy. A comparison between Ti impregnation of the investigated biopsies did not demonstrate any remarkable influence of the surface differences. This can be explained by the fact that only the top diameter and not the implant surface as a whole was the contact area with the excised tissue. Ti in the biopsies was analyzed in terms of its effect histologically and regarding the Ti quantity by spectrophotometry. It was reported that (i) even the highest Ti contamination was observed, it was considered as a negative effect on the mucoperiosteal cover flaps and (ii) the results highlighted the biological acceptance of Ti [76].

The increasing use of commercially pure titanium (CpTi) and the Ti–6Al–4V alloy for material applications in dental and orthopedic implants warrant the study of the storage and elimination of these elements. To understand the *in vivo* storage and elimination of metals, one must first understand the environment and then the metal. The *in vivo* environment is essentially a saline (0.9% NaCl) solution with numerous proteins and enzymes [77]. The pH of an extracellular fluid environment normally ranges from 7.00 to 7.70 [78]. The implantation of a pure metal into a physiological environment may cause it to ionize or form a metal compound. Hamsters were injected with titanium, aluminum, and vanadium salts either intraperitoneally or intramuscularly to study the transport, storage, and elimination of these metals. Blood samples were taken at 4 or 24 h, and urine samples were at 24, 48, and 72 h. The hamsters were then injected weekly for 5 weeks after the initial injection. Blood and portions of the kidneys, liver, lung, and spleen were taken at sacrifice. All samples were analyzed for titanium, aluminum, and vanadium concentrations using graphic furnace atomic adsorption spectroscopy. It was reported that (i) although titanium was not found to be excreted in the urine which might be related to its insolubility in the physiological environment, it was found in low levels in the blood and was elevated over control in the kidney, liver, and spleen, (ii) aluminum detection showed wide standard deviations and high levels in controls; however, aluminum was found to be excreted in the urine and to be transported by the blood in the experimental animals, and a small amount accumulated in the liver and spleen, and (iii) vanadium was excreted in high levels in the urine, being related to its solubility in physiological conditions [78].

6.6 Biocompatibility

The oral environment with saliva and bacteria is corrosive for dental restorative materials. For chemical and biological evaluations, appropriate biological tests and standards have been developed. Such tests and standards, which have been developed in the past 10–15 years, serve as the basis for recommending any dental restorative material. Until a few years ago, almost all national and international dental standards and testing programs focused entirely on physical and chemical properties. Today, however, dental materials standards require biological testing as well. The science of dental materials now encompasses a knowledge and

appreciation of certain biological considerations associated with the selection and use of materials designed for use in the oral cavity. According to existing standards, all dental materials should pass primary tests (screening to indicate cellular response), secondary tests (evaluating tissue responses), and usage tests in animals before being evaluated clinically in humans. Testing programs for dental materials are based on specifications or standards established by national or international standards organizations, such as the American National Standards Institute (ANSI) and International Standards Organization (ISO). The oldest and largest of these programs has been operated continuously by the American Dental Association (ADA) since the late 1920s. Evaluation of dental products for safety and efficacy has historically been the scope of both the ADA and the Food and Drug Administration (FDA). In accordance with these regulations (US Medical Device Amendments, 1976), all dental materials are reviewed for safety and effectiveness, and classified by the FDA as Class I, II, or III. Class I materials are those considered to be of low risk in causing adverse reactions. Materials in Class II must satisfy the requirements outlined in the current ANSI/ADA specifications. The most extensive testing is required for Class III materials, which includes full safety and efficacy assessments prior to marketing. The FDA regulates the components of dental amalgam into Class II (special controls), whereas the United States Pharmacopoeia (USP) grades mercury into Class I (general controls) [79].

Biological compatibility (or in short, biocompatibility) is the ability of a material to perform with an appropriate host response in a specific application. There are three definitions of biocompatibility: (1) the ability of a material to perform with an appropriate host response in a specific application, (2) the quality of not having toxic or injurious effects on biological systems, and (3) comparison of the tissue response produced through the close association of the implanted candidate material to its implant site within the host animal to that tissue response recognized and established as suitable with control materials. All these definitions deal with materials and not with devices. This is a drawback since many medical devices are composed of many materials. Much of the preclinical testing of the materials is not conducted on the devices, but rather on the material itself. At some stage, however, the testing will need to include the device, since the shape and geometry of the device will also affect the biocompatibility [80]. The biocompatibility of a long-term implantable medical device refers to the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host. On the other hand, the biocompatibility of short-term implantable medical device that is intentionally placed within the cardiovascular system for transient diagnostic or therapeutic purposes refers to the ability of the device to carry out its intended function within flowing blood, with minimal interaction between device and blood that adversely affects device performance, and without inducing uncontrolled activation of cellular or plasma protein cascades. Furthermore, the biocompatibility of tissue engineering products (such as a scaffold or matrix) must meet more engineering requirements and refers to the ability to perform as a substrate that will support the appropriate cellular activity, including the facilitation of molecular and mechanical

signaling systems, in order to optimize tissue regeneration, without eliciting any undesirable effects in those cells, or inducing any undesirable local or systemic responses in the eventual host.

There is research on Ti materials focusing on biocompatibility evaluation. Compared with the presently used ($\alpha + \beta$) Ti alloys for medical applications, β -Ti alloys have many advantageous mechanical properties—an improved wear resistance, a high elasticity, and an excellent cold and hot formability—thus promoting their increased application as materials for orthopedic joint replacement. Not all elements with β -stabilizing properties in Ti alloys are suitable for biomaterial applications; corrosion and wear processes cause a release of these alloying elements (Nb, Ta, Ti, Zr, and Al) to the surrounding tissue. Eisenbarth et al. [81] evaluated the biological compatibility of alloying elements for β -Ti and near β -Ti alloys in order to estimate their suitability for biomaterial components, with CpTi (grade II) and the implant steel (316L stainless steel) as reference materials. The investigation included the corrosion properties of the elements, proliferation, mitochondrial activity, cell morphology, and the size of MC3T3-E1 cells and GM7373 cells. It was reported that the biocompatibility range of the investigated metals is (in decreasing biocompatibility): niobium (as a β -phase stabilizing element)→tantalum (as a β -phase stabilizing element)→titanium→zirconium (as an α -phase stabilizing element)→aluminum (as an α -phase stabilizing element)→316L (Mo-containing 18Cr–8Ni stainless steel with low carbon content)→molybdenum [81].

The biocompatibility of metallic implant surfaces is governed in large part by the interfacial kinetics associated with metal release and protein binding. The kinetics of metal release from and protein binding to Co–Cr–Mo and Ti implants (CpTi and Ti–6Al–4V) in human serum were investigated. The studies were carried out by (i) measuring the temporal release of Cr and Ti into serum from Co–Cr–Mo and Ti implants, (ii) examining the composition of human serum proteins adsorbed onto the surfaces of Co–Cr–Mo and Ti implants, and (iii) identifying the serum proteins associated with the binding of soluble Cr and Ti degradation products. It was reported that (i) Cr was released from Co–Cr–Mo implant at an order of magnitude higher than Ti was released from Ti implants, (ii) serum became saturated with soluble Cr and Ti at levels as high as 3250 ng/mL Ti from CpTi, 3750 ng/mL Ti from Ti–6Al–4V, and 35,400 ng/mL Cr from Co–Cr–Mo degradation, and (iii) both Cr and Ti released from Co–Cr–Mo and Ti materials exhibited a bimodal binding pattern to both low-molecular-weight serum protein(s) (< 32 kDa), and to higher molecular weight protein(s) in the 180–250 kDa range. Based on these findings, it was concluded that identification of metal alloy-dependent biofilm compositions and dissolution products provides the basis for understanding the bioavailability and bioreactivity of these implant alloys and their degradation products [82].

Krupa et al. [83] investigated the corrosion resistance and biocompatibility of titanium after surface modification by the ion implantation of calcium, phosphorus, or calcium + phosphorus. Calcium and phosphorus ions were implanted in a dose rate of 10^{17} ions/cm² at the ion beam energy of 25 keV. The corrosion resistance was examined by electrochemical methods in a simulated body fluid

(SBF) at a temperature of 37°C. The biocompatibility was evaluated *in vitro*. The results of the electrochemical examinations (Stern's method) indicated that (i) the calcium, phosphorus, and calcium + phosphorus implantation into the surface of titanium increases its corrosion resistance in stationary conditions after short- and long-term exposures in SBF, (ii) potentiodynamic tests showed that the calcium-implanted samples underwent pitting corrosion during anodic polarization, and (iii) the breakdown potentials measured were high (2.5–3 V) [83], which is unfairly too high when compared to the reasonable range of intraoral potential (0–50 mV) (see Chapter 3). Nayab et al. [84] demonstrated that Ti surfaces implanted with Ca ions can enhance the expression of certain bone-associated components *in vitro* and suggest that this effect could be the cause of potential benefit of this material on bone *in vivo*.

Recently, bioactivity of titanium oxide [85] and porous Ti [86] was evaluated. The titanium oxide films were fabricated on titanium metal by electron-beam deposition technique in various oxygen partial pressures, and the effects of oxygen content in titanium oxide on the bioactivity of titanium implant were evaluated [85]. Raman spectra showed the titanium oxide films had an oxygen-deficient TiO₂ structure. It was concluded that the extent of hydroxyl group formation in simulated body fluid depended on the stoichiometry of TiO₂, which enhanced the bioactivity of titanium [85]. Xue et al. [86], using the laser-engineered net shaping (LENS) method, had fabricated porous Ti implants. It was reported that the thus prepared porous Ti possessed porosity in the range of 17–58 vol.%, pore size up to 800 μm, mechanical strength of 24–463 MPa, and elastic modulus of 2.6–44 GPa. It was further reported that (i) cells spread well on the surface of porous Ti and formed strong local adhesion, and MTT assay indicated LENS-processed porous Ti provides a preferential surface for bone cell proliferation and (ii) porous Ti samples also stimulated faster osteoblast cell differentiation compared with polished Ti sheet, which could be due to the change in cell morphology within the pores of Ti samples. It was recommended that a critical pore size of 200 μm or higher is needed for cell ingrowth into the pores, below which osteoblast cells bridged the pore surface without any growth in the pores [86].

For enhancing the biocompatibility of Ti materials, there are several methods proposed. Li et al. [87] coated a thin hydroxyapatite (HA) layer on a microarc-oxidized titanium substrate by means of the sol–gel method. The HA sol was aged fully to obtain a stable and phase-pure HA, and the sol concentration was varied to alter the coating thickness. Through the sol–gel HA coating, the Ca and P concentrations in the coating layer increased significantly. It was reported that (i) the microarc oxidation (anodizing) enhanced the biocompatibility of the Ti, and the bioactivity was improved further by the sol–gel HA coating on the anodized Ti and (ii) the proliferation and alkaline phosphatase activity of the osteoblast-like cells on the microarc-oxidized Ti/HA sol–gel-treated Ti were significantly higher than those on the microarc-oxidized Ti without the HA sol–gel treatment [87].

Schwarz et al. [88] evaluated the influence of plaque biofilm removal on the mitochondrial activity of human SaOs-2 osteoblasts grown on titanium surfaces. Volunteers wore acrylic splints with structured titanium disks for 72 h to build up

plaque biofilms. Specimens were randomly instrumented using ultrasonic system + chlorhexidine or plastic curettes + CHX. Specimens were incubated with SaOs-2 cells for 6 days. Residual plaque biofilm/clean implant surface areas (%), mitochondrial cell activity (counts/second), and cell morphology were assessed. It was concluded that (i) mitochondrial cell seemed to be impaired by the presence of residual plaque biofilm areas and (ii) its removal alone might not be the crucial step in the reestablishment of the biocompatibility of titanium surfaces [88].

Nitinol- (or NiTi) based shape memory alloys were introduced to medicine in the late 1970s. Despite unique physical, chemical, and mechanical properties associated with NiTi, the wide medical application has been hindered for a long time because of the lack of knowledge of the nature of the biocompatibility of NiTi alloys. A review of biocompatibility with an emphasis on the most recent studies, combined with the results of X-ray surface investigations, allows us to draw conclusions on the origin of the good biological response observed *in vivo*. The tendency of nitinol surfaces to be covered with TiO₂ with only a minor amount of nickel under normal conditions is considered to be responsible for these positive results. A certain type of toxicity, usually observed in *in vitro* studies, may result from the much higher *in vitro* Ni concentrations which are probably not possible to achieve *in vivo*. The essentiality of Ni as a trace element may also contribute to the nitinol (NiTi) biocompatibility within human body tissues [89].

The unique properties of NiTi have provided the enabling technology for many applications in the medical and dental industries, including implants within the bloodstream. Two particularly successful NiTi medical devices are the Simon Nitinol Filter and the Mitek bone suture anchor. The Simon Nitinol Filter is an umbrella-shaped device deployed via the shape memory effect to entrap blood clots in the vena cava. Mitek bone suture anchors have revolutionized the field of orthopedic surgery by providing a secure, stable attachment for tendons, ligaments, and other soft tissue to bone. Based on more than 20 years' successful clinical performance, the excellent biocompatibility, very high corrosion resistance, and excellent cytocompatibility of NiTi has been proven. The nickel in NiTi is chemically joined to the titanium by a strong intermetallic bond, so the risk of reaction, even in patients with nickel sensitivity, is extremely low [90–92]. There are several studies revealing a lower biocompatibility of NiTi under certain conditions [59,93]. The surface preparation techniques have been shown to have a significant effect on the biocompatibility of the alloy [93]. Ion release measurements on NiTi alloy have shown that the initial rate of Ni ion release is high, but falls rapidly within 2 days, which is similar to that of Ni released from 316L stainless steel [56,94], although 316L stainless steel contains only 8 wt%. Armitage et al. [95] mechanically polished NiTi samples, then buff-polished them with diamond paste, and studied the influences of surface modifications on the biocompatibility. For another modification, surfaces were shot-peened with 160 µm spherical glass media, and electropolished in 30% HNO₃ in CH₃OH. It was reported that (i) cytotoxicity and cytocompatibility studies with both fibroblast and endothelial cells showed no differences in the biocompatibility of any of the NiTi surfaces, (ii) the cytotoxicity and cytocompatibility of all surfaces were favorable compared to the untreated

controls, (iii) the hemolysis caused by a range of NiTi surfaces was no different from that caused by polished 316L stainless steel or polished titanium surfaces, (iv) heat treatment (by in-air oxidation at 400°C for 30 min or 600°C for 30 min) of NiTi was found to significantly reduce thrombogenicity to the level of the control, (v) the XPS results showed a significant decrease in the concentration of surface nickel with heat treatment and changes in the surface nickel itself from a metallic to an oxide state, and (vi) the surface contact angle of both preoxidized surfaces appeared much lower (36.3° and 13.5° for 400°C and 600°C oxidation, respectively) than that of polished surfaces (64.6° for buff-polished and 42.5° for electro-polished) [95], indicating that preoxidation makes the Ti surface more active.

Disks consisting of macroporous NiTi alloy are used as implants in clinical surgery for fixation of spinal dysfunctions. Prymak et al. [96] preformed the biocompatibility studies by coincubation of porous NiTi samples with isolated peripheral blood leukocyte fractions (polymorphonuclear neutrophil granulocytes, PMN; peripheral blood mononuclear leukocytes, PBMC) in comparison with control cultures without NiTi samples. The cell adherence to the NiTi surface was analyzed by fluorescence microscopy and SEM. The activation of adherent leukocytes was analyzed by measurement of the released cytokines using enzyme-linked immunosorbent assay. It was found that (i) the cytokine response of PMN (analyzed by the release of IL-1ra and IL-8) was not significantly different between cell cultures with or without NiTi, and (ii) there was a significant increase in the release of IL-1ra, IL-6, and IL-8 from PBMC in the presence of NiTi samples, but (iii) in contrast, the release of TNF- α by PBMC was not significantly elevated in the presence of NiTi, and IL-2 was released from PBMC only in the range of the lower detection limit in all cell cultures [96].

Filip et al. [97] characterized the surface and the bulk structure of NiTi implants by SEM, TEM, XPS, and AES (scanning Auger electron microprobe analysis). NiTi implants were compared with otherwise identically prepared nonimplanted specimens, sputter-cleaned, and reoxidized samples. Nonimplanted and implanted samples had essentially the same surface topography and microstructure. Ti, O, and C were the dominant elements detected on the surface. Trace amounts (~ 1 at.%) of Ni and Ca, N, Si, B, and S were also detected. Ti was present as TiO₂ on the surface, while nickel was present in metallic form. A significant difference in Ni peak intensity was observed when retrieved or nonimplanted control samples (very low nickel content) were compared with sputter-cleaned and reoxidized samples (well-detected Ni). It is mentioned that (i) the method of passivation is crucial for Ni loosening and (ii) no major changes occurred in the NiTi sample bulk structure or in the surface oxide during the implantation periods [97].

Early passive or active motion programs after flexor tendon repair have been shown to be extremely beneficial [98,99]. However, the application of early active motion increases the stress on the repair, leading to a significant number of repair ruptures [100]. It seems that two factors are involved in producing a strong mechanical repair: the technique used and the suture material. Stainless steel has better tensile strength and good knot-holding security, but it is difficult to use and is weakened by kinking [101–104]. NiTi SME alloy has been introduced as a

possible new suture material for flexor tendon surgery [105–107]. NiTi sutures were implanted for biocompatibility testing into the right medial gastrone tendon in 15 rabbits for 2, 6, and 12 weeks. Additional sutures were implanted in subcutaneous tissue for measuring strength in order to determine the effect of implantation on strength properties of NiTi suture material. Braided polyester sutures of approximately the same diameter were used as control. It was found that (i) encapsulating membrane formation around the sutures was minimal in the case of both materials, (ii) the breaking load of NiTi was significantly greater compared to braided polyester, and (iii) implantation did not affect the strength properties of either material [108].

6.7 Biomechanical Compatibility

Biomaterials (especially, implantable materials) must function under biomechanical environments. If there is no compatibility between placed foreign biomaterials and the receiving host tissue, the intended biofunctionality cannot be accomplished. This is one of the three important compatibilities required for successful and biofunctional implants; needless to say, the other two compatibilities are biological compatibility (which has been discussed already) and morphological compatibility (which will be discussed in Chapter 7). [Figure 6.1](#) shows a linear relationship between strength (in terms of yield strength) and rigidity (in terms of modulus of elasticity) among various types of biomaterials. For biomaterials design, engineers need to consider the physiological loads (axial rotation, flexion extension, and lateral bending) to place sufficient structural integrity on the implant [109]. In addition to these parameters, various mechanical properties (elastic modulus, tensile strength, ductility, fatigue life and strength, fretting fatigue life, and wear properties) [110] should be adjusted to suitable levels for structural biomaterials used in implants. Hence, biofunctionality of candidate materials should become a crucial parameter.

Referring to [Figure 6.1](#), we need to discuss some mechanistic concerns related to mechanical environment involved in the implantology; particularly in dental implantology. As described elsewhere, it is normal to employ titanium materials in dental and orthopedic implants. It is expected, right after placement of such implants, for the imbedded implant surface to exhibit solid osteointegration to surrounding tissue (i.e., the placed implant foreign material is biologically fused to the host vital hard/soft tissue after a certain period of time). Hence, the interface is formed by the titanium implant surface and the receiving bone surface. Supposing that the satisfactory level of the osteointegration was established at the interface, a composite structure of titanium implant and bone is now ready to be subjected to a normal mastication (which has normally about 200 N force as a chewing force), and such a composite structure can, as a whole, deform elastically. This situation is called as “strain continuity.” Even though each constituent of the composite (in this case, titanium implant and bone) can bend with equal amounts of elasticity, each

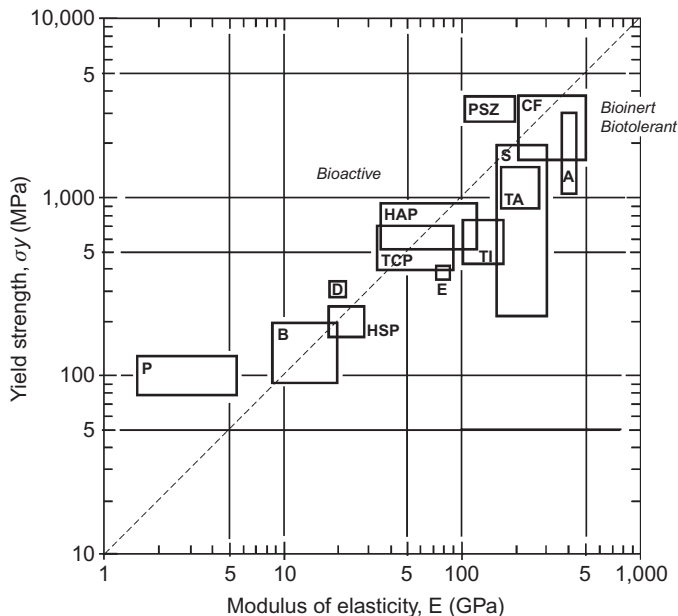


Figure 6.1 Linear relationship between strength and rigidity of various biomaterials in log–log plot. P: polymeric materials, B: bone, HSP: high-strength polymers (Kelvar, Kapton, PEEK), D: dentin, TCP: tricalcium phosphate, HAP: hydroxyapatite, E: enamel, TI: commercially pure titanium (all unalloyed grades), TA: titanium alloys (e.g., Ti–6Al–4V), S: steels (e.g., 304-series stainless steel), A: alumina, PSZ: partially stabilized zirconia, CF: carbon fiber.

one should be experiencing different stress levels, because each possesses distinct level of values of modulus of elasticity (as known as E). According to Figure 6.1, we can estimate that E for bone can be around 15 GPa whilst that of titanium is around 150 GPa, which the latter is one decade larger than the former. As Hooke's law states, the stress on titanium is $\sigma_T = E_T \times \varepsilon_T$ and for bone, $\sigma_B = E_B \times \varepsilon_B$. Since, as indicated before, the strain should be continuous, $\varepsilon_T = \varepsilon_B$, and because $E_T > E_B$, σ_T should be much larger than σ_B . This mechanistic situation is called as “discrete stress.” Let the difference between these stresses $\Delta\sigma = \sigma_T - \sigma_B$. When such stress difference $\Delta\sigma$ happens to be bigger than the interfacial bonding (or fused) strength, the original interfacial bonding between T and B should be debonded, apparently resulting in failure of the placed implant. Now, it is well documented that hydroxyapatite coating onto titanium implant substrates will promote and assist early stages of osteointegration. But, once again referring to Figure 6.1, HAP (hydroxyapatite) is positioned between T and B materials, indicating that HAP material can perform a mechanical buffering function. This is a good example of hindsight. Further, current ceramic materials have been used for implant fabrication: single crystals of alumina [111,112], polycrystals of zirconia [113,114,115], titania [116] or combinations of both [117]. One remarkable

advantage of these ceramic implants is due to their esthetic appearance of a bright white color. Again referring to Figure 6.1, we can identify these ceramics (PSZ and A) at further away from T group, suggesting that the potential interfacial stress, $\Delta\sigma$, could be much higher than previous $\Delta\sigma$ generated between T and B. It is crucial that this higher risk for interfacial debonding or even fracture on ceramic implants or alveolar bone should be carefully taken into consideration when ceramic implants are placed.

The lower premolars of 6 beagle dogs were extracted and the ridges were allowed to heal for 8 weeks [118]. Thirty-six implants were bilaterally placed, remaining for 1 and 3 weeks. Used implant systems were as follows: group A: Ti–6Al–4V with a dual acid-etched surface with nanometer scale discrete crystalline deposition; group B: Ti–6Al–4V with a titanium oxide-blasted fluoride-modified surface chemistry; and group C: Ti–6Al–4V with a bioceramic microblasted surface. After each 1 and 3 weeks, implants were torque-tested to interface failure and histologically evaluated. It was reported that (i) torque values were significantly affected by time and implant types and (ii) highest to lowest order for torque value was from group C, group B to group A [118].

Metallic implantation materials having high yield strength, low elastic modulus, and noncytotoxic alloying elements would be advantageous for the long-term stability of implants [119]. The ultrafine-grained (0.3 μm) Ti–13Nb–13Zr was prepared by dynamic globularization without any severe deformation to assess the *in vitro* osteoconductivity. It was indicated that dynamic globularized ultrafine-grained Ti–13Nb–13Zr alloy was promising for load-bearing endosseous implant material because of its excellent mechanical and biological compatibilities [119].

One important variable in the role of bone remodeling is the difference in modulus of elasticity between bone and its replacement [120]. Normally, the larger the difference, the more rapidly bone changes take place. Ti is particularly good in this regard because of its lower modulus of elasticity [121]. However, this is not true when the above mechanical environment is concerned. Medical-grade titanium samples were examined using X-ray photoelectron spectroscopy before and after immersion in various proteins. Additionally, an implant removed from a patient following clinical failure was examined using scanning ion and electron microscopy. The surface of the as-received sample was found to be mainly TiO_2 , with contaminations of $\text{H}_2\text{O}/\text{OH}^-$, and also calcium and nitrogen, which remained after autoclaving. The failed clinical sample was found to be partially fibrously encapsulated, with evidence of calcification. Small amounts of TiOOH were detected at the fibrous periphery [121], supporting the theory of Tengvall et al. [122,123].

The surface layer of implants should be biomechanically compatible with the mechanical properties of vital soft/hard tissues, as mentioned before. For accomplishing this specific aim, we have already discussed that coating of the material (with HAP or TCP) is very effective. Another technique was introduced by Asaoka et al. [124], who prepared titanium powder with a granule diameter of 420–500 μm and fabricated porous titanium specimens made from this powder. The mechanical properties of these specimens were examined. It was reported that (i) the compressive strength and low cyclic compressive fatigue strength were 182

and 40 MPa, respectively, (ii) the compressive strength of the porous-titanium-coated dental implants was 230 MPa, but fatigue strength was not improved. The possibility of using porous titanium on dental implant can be considered with respect to biomechanical compatibility and strength, and (iii) materials with an elastic modulus of 70–200 GPa have most frequently been used for dental implants, but porous titanium has a lower elastic modulus than this value; however, (iv) a thick core with an ingrowth of tissue into void channels raises the elastic modulus of the material [124].

Once a biomechanical compatibility is established, the placed implant needs to bond and incorporate firmly to the surrounding tissue structure. There are four basic methods to fix implants to bone. The *first* method is based on modifying the implant's surface form and texture to promote fixation by mechanical interlocking on the macro- or microscale. For example, plasma-sprayed coatings of metal or other materials (including ceramics) on their surface promote macro- and microinterlock. The *second* basic method of bone-implant fixation involves the use to some type of "bioactive" biomaterials for the implant, either as a surface coating or as the bulk material, to promote stronger bone-implant attachment through the physical and/or chemical bonding between implant surface and tissue constituents. The *third* fixation concept is "osteointegration," which indicates a direct structural and functional connection between vital bone and the surface of a load-carrying implant through the macro- as well as microinterlocking. In the last few years, the main advancements in implantology were achieved by creating optimal surface qualities of dental implants. New osteoinductive and osteoconductive surfaces have been developed [125–130]. The reason for working on an optimal surface was to achieve a better result of osteointegration and therefore a better long-term stability of dental implants. To achieve a full osteointegration and good periimplant gingival was the main task of scientific work. Good periimplant gingival has a protective function for the bone-implant interface [52,58]. The *fourth* fixation concept is "fibro-osteointegration" ("pseudo-periodontal ligament"). This is a connection of implant to tissue by means of a region of nonmineralized connective tissue which forms adjacent to the implant and attaches it to surrounding bone [131].

While it is known that dental implants can work due to the osteointegration, implants can also fail. In designing a successful dental implant, the main objective is to ensure that the implant can support biting forces and deliver them safely to interfacial tissues over the long term. Biomechanics are central in this design problem. Key topics include: (i) the nature of the biting forces on the implants, (ii) how the biting forces are transferred to the interfacial tissues, and (iii) how the interfacial tissues react, biologically, to stress transfer conditions. For biting forces on dental implants, the basic problem is to determine the *in vivo* loading components on implants in various prosthetic situations, e.g., for implants acting as single tooth replacements or as multiple supports of loaded bridgework. Significant progress has been made as several theoretical models have been presented for determining the partitioning of forces among dental implants supporting bridgework. Interfacial stress transfer and interfacial biology represent more difficult problems. While many engineering studies have shown that variables such as implant shape, elastic

modulus, extent of bonding between implant, and bone can affect the stress transfer conditions, the unresolved question is whether there is any biological significance to such differences. Recent research suggests that the research for a more detailed hypothesis regarding the relationship between interface mechanics and biology should take into account basic bone physiology, e.g., wound healing after implantations plus basic processes of bone modeling and remodeling [132]. The successful clinical results achieved with osseointegrated dental implants underscore the fact that such implants easily withstand considerable masticatory loads. In fact, one study showed that bite forces in patients with these implants were comparable to those in patients with natural dentitions. Studies of the interface between titanium implants and bone show that a close contact with a titanium implant develops during the healing period. It is important to analyze macroscopic stress distribution and load transfer mechanisms where close apposition of bone to titanium implants is provided at the microscopic level. The close apposition of bone to the titanium implant is the essential feature that allows a transmission of stress from the implant to the bone without any appreciable relative motion or abrasion. The absence of any intermediate fibrotic layer allows stress to be transmitted without any progressive change in the bond or contact between the bone and the implant. The osteointegrated implant provides a direct contact with bone and therefore will transmit any stress waves or shocks applied to the fixtures. For this reason, it is advisable to use a shock-absorbing material such as acrylic resin in the form of acrylic resin artificial teeth in the fixed partial denture. This arrangement allows for the development of a stiff and strong substructure with adequate shock protection on its outer surface [131].

Since dental implants must withstand relatively large forces and moments in function, a better understanding of *in vivo* bone response to loading would aid implant design. Brunski [133] pointed out that the following topics are essential in this problem: (i) theoretical models and experimental data are available for understanding implant loading as an aid to case planning, (ii) at least for several months after surgery, bone healing in gaps between implant and bone, as well as in preexisting damaged bone, will determine interface structure and properties, (iii) an interfacial cement line exists between the implant surface and the bone for titanium and hydroxyapatite, (iv) excessive interfacial micromotion early after implantation interferes with local bone healing and predisposes the implants to a fibrous tissue interface instead of osseointegration, and (v) large strains can damage bone. For implants that have healed *in situ* for several months before being loaded, data support the hypothesis that interfacial overload occurs if the strains are excessive in interfacial bone [133].

Beside the surface qualities, there are other important factors for achieving perfect periimplant bone and gingival conditions. In most cases, eccentric forces, overloading of implants, and stress forces are the main reasons for periimplant bone loss in the crestal region, and therefore bad periimplant results. Thus, it is important to avoid large and eccentric forces to prevent periimplant bone damage. In some cases, it is not possible to avoid small tension forces caused by technical production of superstructures. This tension can only be minimized by bio-kinetic

abutments positioned in the implant neck region. These “intramobile elements” were used in recent years as interpolated silicon shock-absorbing elements [132,134–136]. The silicon abutments were in direct contact with the periimplant gingival, although this material is not suited as a bio-inert implant material in this region. Therefore, it is necessary to develop a new implant system with good surface qualities in the intraosseous and trans-gingival region that includes a central shock-absorbing element without contact with the periimplant region. It was reported that good functional properties are essential in dental implantology. Bio-kinetic elements are imitating dental resilience. The mobile implant (SIS Inc., Klagenfurt, Australia) is a self-cutting conical screw implant with an integrated bio-kinetic element. The shock absorber is a central part of the implant and a titanium ring closes the shock-absorbing unit within the implant. The resilience of the implant was tested by axial and horizontal loading in a special testing unit. Furthermore, a survival test of the elastic titanium ring in the most exposed cervical part of the implant was performed. After the region was examined by electron microscopy after 122 million movements in the axial and horizontal direction, it was reported that (i) a progressive shock absorption was registered during horizontal and axial movements, (ii) the maximum movements were 0.06 mm in the axial and 0.16 mm in horizontal direction, and (iii) no signs of material destruction were observed in the electron microscopic analysis [137].

Lastly, due to significant differences between natural tooth and placed implant material in mechanical properties at the interfaces, it has been emphasized how important it is to ensure the mechanical compatibility at the interface between placed implant and receiving hard tissue. But this argument should not be limited to a single unit implant case; it should also be applied to clinically connecting implanted teeth and natural healthy teeth, which would be more challenging.

References

- [1] Venugopal B, Luckey TD. Metal toxicity in mammals. London, UK: Plenum Press; 1978.
- [2] Plenk H, Zitter H. Material considerations. In: Watzek G, editor. Endosseous implants: scientific and clinical aspects. Chicago, IL: Quintessence Publishing; 1996.
- [3] Lemons JE. Dental implant retrieval analyses. *J Dent Educ* 1988;52:748–56.
- [4] Lemons JE, Lucas LC, Johansson B. Intraoral corrosion resulting from coupling dental implants and restorative metallic systems. *Implant Dent* 1992;1:107–12.
- [5] Zitter H, Plenk H. The electrochemical behavior of metallic implant materials as an indicator of their biocompatibility. *J Biomed Mater Res* 1987;21:881–96.
- [6] Schroeder A, Sutter F, Krekeler G. Oral implantology. New York, NY: Georg Thieme Verlag Stuttgart; 1991. pp. 45–48
- [7] Sakurai H. Why are metals important to human body? Tokyo: Kodansha; 2000. pp. 59–65
- [8] Fuwa K. Living organisms and heavy metals. Tokyo: Kodansha-Scientific; 1980. pp. 33–56
- [9] Hallab NJ, Anderson S, Caicedo M, Brasher A, Mikecz K, Jacobs JJ. Effects of soluble metals on human peri-implant cells. *J Biomed Mater Res* 2005;74A:124–40.

- [10] Maurer AM, Merritt K, Brown SA. Cellular uptake of titanium and vanadium from addition of salts or fretting corrosion *in vitro*. J Biomed Mater Res 1994;28:241–6.
- [11] Evans EJ, Benjamin M. The effect of grinding conditions on the toxicity of cobalt–chrome–molybdenum particles *in vitro*. Biomaterials 1987;8:377–84.
- [12] Yang RS, Tsai KS, Liu SH. Titanium implants enhance pulmonary nitric oxide production and lung injury in rats exposed to endotoxin. J Biomed Mater Res 2004;69A:561–6.
- [13] Shanbhag A, Jacobs JJ, Black J, Galante JO, Glant TT. Macrophage/particle interactions: effects of size, composition and surface area. J Biomed Mater Res 1994;28:81–90.
- [14] Takeda K, Shinkai Y, Suzumi K, Yanagita S, Umezawa M, Yokota S, et al. Health effects of nanomaterials on next generation. Pharm Soc Jpn 2011;131:229–36.
- [15] Kumazawa R, Watari F, Takashi N, Tanimura Y, Uo M, Totsuka Y. Effects of Ti ions and particles on neutrophil function and morphology. Biomaterials 2002;23:3757–64.
- [16] Harris LG, Patterson LM, Bacon C, Gwynn I, Richards RG. Assessment of the cytocompatibility of different coated titanium surfaces to fibroblasts and osteoblasts. J Biomed Mater Res 2005;73A:12–20.
- [17] Yamamoto A, Honma R, Sumita M. Cytotoxicity evaluation of 43 metal salts using murine fibroblasts and osteoblastic cells. J Biomed Mater Res 1998;39:331–40.
- [18] Yamamoto A, Kobayashi T, Sumita M, Yamamoto A, Hanawa T. Mutagenicity evaluation of forty-one metal salts by the *umu* tests. J Biomed Mater Res 2002;59:176–83.
- [19] Okazaki Y, Gotoh E. Effect of metal released from Ti alloy wear powder on cell viability. Mater Trans JIM 2000;41:1247–55.
- [20] Yamamoto A, Honma R, Sumita M, Hanawa T. Cytotoxicity evaluation of ceramic particles of different sizes and shapes. J Biomed Mater Res 2004;68A:244–56.
- [21] Mu Y, Kohyama Y, Hanawa T. Metal ion releases from titanium with active oxygen species generated by rat macrophages *in vitro*. J Biomed Mater Res 2000;49:238–43.
- [22] Manceur A, Chellat F, Merhi Y, Chumlyakov Y, Yahia L'H. *In vitro* cytotoxicity evaluation of a 50.8% NiTi single crystal. J Biomed Mater Res 2003;67A:641–6.
- [23] Bordji K, Jouzeau JY, Mainard D, Payan E, Netter P, Rie KT, et al. Cytocompatibility of Ti–6Al–4V and Ti–5Al–2.5Fe alloys according to three surface treatments, using human fibroblasts and osteoblasts. Biomaterials 1996;17:929–40.
- [24] Wever DJ, Veldhuizen AG, Sanders MM, Schakenraad JM. Cytotoxic, allergic and genotoxic activity of a nickel–titanium alloy. Biomaterials 1997;18:1115–20.
- [25] Yeung KWK, Poon JWY, Liu XY, Ho JPY, Chung CY, Chu PK, et al. Investigation of nickel suppression and cytocompatibility of surface-treated nickel–titanium shape memory alloys by using plasma immersion ion implantation. J Biomed Mater Res 2005;72A:238–45.
- [26] Yeung KWK, Poon RWY, Liu XY, Ho JPY, Chung CY, Chu PK, et al. Corrosion resistance, surface mechanical properties, and cyto-compatibility of plasma immersion ion implantation-treated nickel–titanium shape memory alloys. J Biomed Mater Res 2005;75A:256–67.
- [27] Fukushima O, Yoneyama T, Doi H, Hanawa T. Corrosion resistance and surface characterization of electrolyzed Ti–Ni alloy. Dent Mater J 2006;25:151–60.
- [28] Tada H, Shibo O, Kuroshima K, Koyama M, Tsukamoto K. An improved colorimetric assay for interleukin-2. Immunol Methods 1986;93:157–65.
- [29] Es-Souni M, Es-Souni M, Brandies HF. On the transformation behavior, mechanical properties and biocompatibility of two NiTi-based shape memory alloys: NiTi₄₂ and NiTi₄₂Cu₇. Biomaterials 2001;22:2153–61.

- [30] Niinomi M. Fatigue performance and cyto-toxicity of low rigidity titanium alloy, Ti–29Nb–13Ta–4.6Zr. *Biomaterials* 2003;24:2673–83.
- [31] Borenfreund E, Purener JA. Toxicity determined *in vitro* by morphological alternations and neutral absorption. *Toxicol Lett* 1985;24:119–24.
- [32] Mosman T. Rapid colorimetric assay for cellular growth and survival, application of proliferation and cytotoxicity assay. *J Immunol Methods* 1983;65:55–63.
- [33] Spriano S, Bosetti M, Bronzoni M, Vernè E, Maina G, Bergo V, et al. Surface properties and cell response of low metal ion release Ti–6Al–7Nb alloy after multi-step chemical and thermal treatments. *Biomaterials* 2005;26:1219–29.
- [34] Hou X, Weiler A, Winger JN, Morris JR, Borke JL. Rat model for studying tissue changes induced by the mechanical environment surrounding titanium implants. *Int J Oral Maxillofac Implants* 2009;24:800–7.
- [35] Kang MK, Moon SK, Kim KM, Kim KN. Antibacterial effect and cytocompatibility of nano-structured TiO₂ film containing Cl. *Dent Mater J* 2011;39:790–8.
- [36] Olmedo DG, Tasat DR, Evelson P, Guglielmotti MB, Cabrini RL. Biological response of tissues with macrophagic activity to titanium dioxide. *J Biomed Mater Res A* 2008;84:1087–93.
- [37] Rupp F, Scheideler L, Eichler M, Geis-Gerstorfer J. Wetting behavior of dental implants. *Int J Oral Maxillofac Implants* 2011;26:1256–66.
- [38] Wood JFL. Patient sensitivity to alloy used in partial denture. *Br Dent J* 1974;136:423–4.
- [39] Menne T, Christophersen J, Green A. Epidemiology of nickel dermatitis. In: Maibach HI, Menne T, editors. *Nickel and the skin: immunology and toxicology*. Boca Raton, FL: CRC Press; 1989. p. 109–16.
- [40] Romaguera C, Grimalt F, Vilaplana J. Contact dermatitis from nickel: an investigation of its source. *Contact Dermatitis* 1988;19:52–7.
- [41] Meijer C, Bredberg M, Fischer T, Widstrom L. Ear piercing and nickel and cobalt sensitization, in 520 young Swedish men doing compulsory military service. *Contact Dermatitis* 1995;32:147–79.
- [42] Gammelgaard B, Fullerton A, Avnstorp C, Menne T. Permeation of chromium salts through human skin *in vitro*. *Contact Dermatitis* 1992;27:302–10.
- [43] Peters MA, Schroeter AL, van Hale HM, Broadbent JC. Pacemaker contact sensitivity. *Contact Dermatitis* 1984;11:214–22.
- [44] Laylor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA. Sensitivity to titanium. A case of implant failure? *J Bone Joint Surg* 1991;73:25–8.
- [45] Magnusson B, Kligman AM. The identification of contact allergens by animal assay. The Guinea pig maximization test. *J Invest Dermatol* 1969;52:268–76.
- [46] Goodwin BJG, Crecel RWR, Johnson AW. A comparison of three guinea-pig sensitization procedures for the detection of 19 reported human contact sensitizers. *Contact Dermatitis* 1981;7:248–58.
- [47] Mor S, Ben-Efraim S, Leibovici J, Ben-David A. Successful contact sensitization to chromate in mice. *Int Arch Allergy Apply Immunol* 1988;85:452–7.
- [48] Vreeburg KJJ, de Groot K, van Hoogstraten IMW, von Blomberg BME, Scheper RJ. Successful induction of allergic contact dermatitis to mercury and chromium in mice. *Int Arch Allergy Apply Immunol* 1991;96:179–83.
- [49] Basketter DA, Sholes EW. Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens. *Fd Chem Toxicol* 1992;30:65–9.

- [50] Samits MH, Katz SA, Sheiner DM, Lewis JE. Attempts to induce sensitization in guinea pigs with nickel complexes. *Acta Dermato-Venereologica* 1975;55:478–80.
- [51] Moller H. Attempts to induce contact allergy to nickel in the mouse. *Contact Dermatitis* 1984;10:65–8.
- [52] Rohold AE, Nielsen GD, Andersen KE. Nickel-sulfate-induced dermatitis in the guinea pig maximization test: a dose–response study. *Contact Dermatitis* 1991;24:35–9.
- [53] Zissu D, Cavelier C, De Ceaurriz J. Experimental sensitization of guinea-pigs to nickel and patch testing with metal samples. *Fd Chem Toxicol* 1987;25:83–5.
- [54] Ikarashi Y, Momma J, Tsuchiya T, Nakamura A. Evaluation of skin sensitization potential of nickel, chromium, titanium and zirconium salts using guinea-pigs and mice. *Biomaterials* 1996;17:2103–8.
- [55] Harzer W, Schröter A, Gedrange T, Muschter F. Sensitivity of titanium brackets to the corrosive influence of fluoride-containing toothpaste and tea. *Angle Orthod* 2001;71:318–23.
- [56] Ryhanen J, Niemi E, Serlo W, Niemela E, Sandvik P, Pernu H, et al. Biocompatibility of nickel titanium shape memory metal and its corrosion behavior in human cell cultures. *J Biomed Mater Res* 1997;35:451–7.
- [57] McKay GC, Macnair R, MacDonald C, Grant MH. Interactions of orthopaedic metals with an immortalized rat osteoblast cell line. *Biomater* 1996;17:1339–44.
- [58] Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, Hensten-Pterson A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop* 1996;109:148–54.
- [59] Berger-Gorbet M, Broxup B, Rivard C, Yahia L'H. Biocompatibility testing of NiTi screw using immuno histochemistry on sections containing metallic implants. *J Biomed Mater Res* 1996;32:243–8.
- [60] Bass JK, Fine H, Cisneros GJ. Nickel hypersensitivity in the prosthodontics patient. *Am J Orthod Dentofacial Orthop* 1993;103:280–5.
- [61] Rogers SD, Howie DW, Graves SE, Percy MJ, Haynes DR. *In vitro* human monocyte response to wear particles of titanium alloy containing vanadium or niobium. *J Bone Joint Surg* 1997;79B:311–5.
- [62] Horowitz SM, Luchetti WT, Gonzales JB, Ritchie CK. The effects of cobalt chromium upon macrophages. *J Biomed Mater Res* 1998;41:468–73.
- [63] Schmalz G, Schuster U, Schweikl H. Influence of metals in IL-6 release *in vitro*. *Biomaterials* 1998;19:1689–94.
- [64] Burden DJ, Eedy DJ. Orthodontic headgear related to allergic contact dermatitis: a case report. *Br Dent J* 1991;170:447–8.
- [65] Veien NK, Borchorst E, Hattel T, Laurberg G. Stomatitis or systemically induced contact dermatitis from metal wire in orthodontic materials. *Contact Dermatitis* 1994;30:210–3.
- [66] Torgerson S, Gjerdet NR, Erichsen ES, Bang G. Metal particle and tissue changes adjacent to miniplates. A retrieval study. *Acta Odontol Scand* 1995;53:65–71.
- [67] Alpert B, Seligson D. Removal of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;54:618–21.
- [68] Mjoberg B, Hellquist E, Mallmin H, Lindh U. Aluminum, Alzheimer's disease and bone fragility. *Acta Orthop Scand* 1997;68:511–4.
- [69] Boyce BF, Byars J, McWilliams S, Mocan MZ, Elder HY, Boyle IT, et al. Histological and electron microprobe studies of mineralization in aluminum-related osteomalacia. *J Clin Pathol* 1992;45:502–50.

- [70] Zaffe D, Bertoldi C, Consolo U. Accumulation of aluminum in lamellar one after implantation of titanium plates, Ti–6Al–4V screws, hydroxyapatite granules. *Biomaterials* 2004;25:3837–44.
- [71] Williams DF. Biological effects of titanium. In: Willimas DF, editor. *Systemic aspects of biocompatibility*. Boca Raton, FL: CRC Press; 1981. p. 169–78.
- [72] Schroeder HA, Bolassa JJ, Hipton IH. Abnormal trace metals in man: titanium. *J Chronic Dis* 1963;16:55–72.
- [73] Williams DF. The properties of titanium and its uses in cardiovascular surgery. *J Cardiovasc Technol* 1978;20:52–65.
- [74] Olmedo DG, Feriández MM, Guglielmotti MB, Cabrini RL. Macrophages related to dental implant failure. *Implant Dent* 2003;12:75–80.
- [75] Olmedo DG, Tasat DR, Guglielmotti MB, Cabrini RL. Effect of titanium dioxide on the oxidative metabolism of alveolar macrophages: an experimental study in rats. *J Biomed Mater Res* 2005;73A:142–9.
- [76] Schlegel KA, Eppeneder S, Wiltfang J. Soft tissue findings above submerged titanium implants—a histological and spectroscopic study. *Biomaterials* 2002;23:2939–44.
- [77] Merritt K, Margevicius RW, Brown SA. Storage and elimination of titanium, aluminum, and vanadium salts, *in vivo*. *J Biomed Mater Res* 1992;26:1503–15.
- [78] Ganong WF. Regulation of extracellular fluid composition and volume. Review of medical physiology. 12th ed. Los Altos, CA: Lange Medical Pub; 1985. p. 104
- [79] Anusavice KJ. Phillips' science of dental materials. Boca Raton, FL: Saunders: An Imprint of Elsevier; 2003. pp. 185–196
- [80] Williams DF. Revisiting the definition of biocompatibility. *Med Device Technol* 2003;14:10–3.
- [81] Eisenbarth E, Velten D, Müller M, Thull R, Breme J. Biocompatibility of β -stabilizing elements of titanium alloys. *Biomaterials* 2004;25:5705–13.
- [82] Hallab NJ, Skipor A, Jacobs JJ. Interfacial kinetics of titanium- and cobalt-based implant alloys in human serum: metal release and biofilm formation. *J Biomed Mater Res* 2003;65A:311–8.
- [83] Krupa D, Baszkiewicz J, Kozubowski JA, Lewandowska-Szumieł M, Barcz A, Sobczak JW, et al. Effect of calcium and phosphorous ion implantation on the corrosion resistance and biocompatibility of titanium. *J Biomed Mater Eng* 2004;14:525–36.
- [84] Nayab SN, Jones FH, Olsen I. Effects of calcium-implantation of titanium on bone cell function *in vitro*. *J Biomed Mater Res A* 2007;83:296–302.
- [85] Jeong SH, Park YJ, Kim BS, Song HJ. Effects of oxygen content on bioactivity of titanium oxide films fabricated on titanium by electron beam evaporation. *J Nanosci Nanotechnol* 2007;7:3815–8.
- [86] Xue W, Krishna BV, Bandyopadhyay A, Bose S. Processing and biocompatibility evaluation of laser processed porous titanium. *Acta Biomater* 2007;3:1007–18.
- [87] Li L-H, Kim H-W, Lee S-H, Kong Y-M, Kim K-E. Biocompatibility of titanium implants modified by microarc oxidation and hydroxyapatite coating. *J Biomed Mater Res* 2005;73A:48–54.
- [88] Schwarz F, Papanicolaou P, Rothamel D, Beck B, Herten M, Becker J. Influence of plaque biofilm removal on reestablishment of the biocompatibility of contaminated titanium surfaces. *J Biomed Mater Res* 2006;77A:437–44.
- [89] Shabalovskaya SA. On the nature of the biocompatibility and on medical applications of NiTi shape memory and superelastic alloys. *J Biomed Mater Eng* 1996;6:267–89.

- [90] Ryhanen J. Biocompatibility evaluation of nickel–titanium shape memory metal alloy. <<http://herkules.oulu.fi/isbn9514252217>>
- [91] Oshida Y, Miyazaki S. Corrosion and biocompatibility of shape memory alloys. *Corr Eng* 1991;40:1009–25.
- [92] Castleman LS, Motzkin SM. Biocompatibility of Nitinol. In: Williams DF, editor. *Biocompatibility of clinical implant materials*. Philadelphia, PA: CRC Press; 1981. p. 129–54.
- [93] Assad M, Lomardi S, Bernèche S, DesRosiers EA, Yahia L'H, Rivard CH. Cytotoxicity testing of the nickel titanium shape memory alloy. *Ann Chir* 1994;48:731–6.
- [94] Wever DJ, Veldhuizen AG, deVries J, Busscher HJ, Uges DRA, van Horn JR. Electro-chemical and surface characterization of a nickel titanium alloy. *Biomaterials* 1998;19:761–6.
- [95] Armitage DA, Parker TL, Grant DM. Biocompatibility and hemocompatibility of surface-modified NiTi alloys. *J Biomed Mater Res* 2003;66A:129–37.
- [96] Prymak O, Bogdanski D, Köller M, Esenwein SA, Muhr G, Beckmann F, et al. Morphological characterization and *in vitro* biocompatibility of a porous nickel–titanium alloy. *Biomaterials* 2005;26:5801–7.
- [97] Filip P, Lausmaa J, Musialek J, Mazanec K. Structure and surface of NiTi human implants. *Biomaterials* 2001;22:2131–8.
- [98] Elliot D, Moiemien NS, Flemming AF, Harris SB, Foster AJ. The rupture rate of acute flexor tendon repairs mobilized by the controlled actions motion regimen. *J Hand Surg* 1994;19B:607–12.
- [99] Gelberman RH, Amifl D, Gonsalves M, Woo S, Akeson WH. The influence of protected passive mobilization on the healing of flexor tendons: a biochemical and minoangio-graphic study. *Hand* 1981;13:120–8.
- [100] Small JO, Brennan MD, Colville J. Early active mobilization following flexor tendon repair in zone 2. *J Hand Surg* 1989;14B:383–91.
- [101] Trail IA, Powell ES, Noble J. An evaluation of suture materials used in tendon surgery. *J Hand Surg* 1989;14B:422–7.
- [102] Nystrom B, Holmlund D. Separation of sutured tendon ends when different suture techniques and different suture materials are used. An experimental study in rabbits. *Scand J Plast Reconstr Surg* 1983;17:19–23.
- [103] Silfrerskiöld KI, Andersson CH. Two new methods tendon repair: an *in vitro* evaluation of tensile strength and gaps formation. *J Hand Surg* 1993;18A:58–65.
- [104] Aoki A, Manske PR, Pruitt DL, Larson BJ. Tendon repair using flexor tendon splints: an experimental study. *J Hand Surg* 1994;19A:984–90.
- [105] Moneim MS, Firoozbakhsh K, Mustapha AA, Larsen K, Shahinpoor M. Flexor tendon repair using shape memory alloy suture: a biomechanical evaluation. *Clin Orthop* 2002;402:251–9.
- [106] Miura F, Mogi M, Ohura Y, Hamanaka H. The super-elastic property of the Japanese NiTi alloy wire for use in orthodontics. *Am J Orthod Dentofacial Orthop* 1986;90:1–10.
- [107] Duerig TW, Pelton AP, Stockel D. The utility of superelasticity in medicine. *J Biomed Mater Eng* 1996;6:255–66.
- [108] Kujala S, Pajala A, Kallioinen M, Pramila A, Tuukkanen J, Ryhänen J. Biocompatibility and strength properties of nitinol shape memory alloy suture in rabbit tendon. *Biomaterials* 2004;25:353–8.

- [109] Zivić F, Babić M, Grujović N, Mitrović S. Tribometry of materials for bioengineering applications. *Tribol Industry* 2010;32:25–32.
- [110] Niimomi M. Mechanical biocompatibility of titanium alloys for biomedical applications. *J Mech Behav Biomed Mater* 2008;1:30–42.
- [111] Treccani L, Maiwald M, Zöllmer V, Busse M, Grathwohl G, Rezwan K. Antibacterial and abrasion-resistant alumina micropatterns. *Adv Eng Mater* 2009;11:B61–6.
- [112] Lin Y-S, Burggraaf AJ. Preparation and characterization of high-temperature thermally stable alumina composite membrane. *J Am Ceram Soc* 1991;74:219–24.
- [113] Liu Y, Chen OY, Wei CC, Li K. Preparation of yttria-stabilised zirconia (YSZ) hollow fibre membranes. *Desalination* 2006;199:360–2.
- [114] Wenz HJ, Bartsch J, Wolfart S, Kern M. Osseointegration and clinical success of zirconia dental implants: a systematic review. *Int J Prosthodont* 2008;21(1):27–36.
- [115] Fernández-Fairén M, Sala P, Gil FJ. Failures of yttria-stabilised tetragonal zirconia: 52 retrieved ceramic femoral heads of total hip prostheses. *Biomed Mater Eng* 2006;16:415–22.
- [116] Schincaglia GP, Marzola R, Scapoli C, Scotti R. Immediate loading of dental implants supporting fixed partial dentures in the posterior mandible: a randomized controlled split-mouth study: machined versus titanium oxide implant surfaces. *Int J Oral Maxillofac Implants* 2007;22:35–46.
- [117] Domanski M, Winnubst L, Luttge R, Lamers E, Walboomers XF, Jansen J, et al. Production and characterization of micro- and nano-features in biomedical alumina and zirconia ceramics using a tape casting route. *J Mater Sci Mater Med* 2012;23:1637–44.
- [118] Coelho PG, Granato R, Marin C, Bonfante EA, Freire JN, Janal MN, et al. Biomechanical evaluation of endosseous implants at early implantation times: a study in dogs. *J Oral Maxillofac Surg* 2010;68:1667–75.
- [119] Park CH, Lee CS, Kim YJ, Jang JH, Suh JY, Park JW. Improved pre-osteoblast response and mechanical compatibility of ultrafine-grained Ti–13Nb–13Zr alloy. *Clin Oral Implants Res* 2011;22:735–42.
- [120] Williams DF. The biological applications of titanium and titanium alloys. In: Kossowsky R, et al., editors. *Materials science and implant orthopaedic surgery*. Dordrecht, the Netherlands: Martinus Nijhoff; 1986. p. 107–16.
- [121] Sutherland DS, Forshaw PD, Allen GC, Brown IT, Williams KR. Surface analysis of titanium implants. *Biomaterials* 1993;14:893–9.
- [122] Tengvall P, Lundstrom I, Sjoqvist L, Elwing H. Titanium–hydrogen peroxide interactions: model studies of the influence of the inflammatory response on titanium implants. *Biomaterials* 1989;10:166–75.
- [123] Tengvall P, Lundstrom I. Physio-chemical considerations of titanium as a biomaterial. *Clin Mater* 1992;9:115–34.
- [124] Asaoka K, Kuwayama N, Okuno O, Miura I. Mechanical properties and bio-mechanical compatibility of porous titanium for dental implants. *J Biomed Mater Res* 1985;19:699–713.
- [125] Cole BJ, Bostrom MP, Pritchard TL, Summer DR, Tomin E, Lane JM, et al. Use of bone morphogenetic protein 2 on ectopic porous coated implants in the rat. *Clin Orthop* 1997;345:219–28.
- [126] Denissen H, van Beek E, van den Bos T, de Bleeck J, Klein C, van den Hooff A. Degradable biphosphonate-alkaline phosphatase-complexed hydroxyapatite implants in vitro. *J Bone Miner Res* 1997;12:290–7.

- [127] Piztelli A, Scarano A, Di Alberti L, Piatelli M. Histological and histochemical analyses of acid and alkaline phosphatase around hydroxyapatite-coated implants: a time course study in rabbit. *Biomaterials* 1997;18:1191–4.
- [128] Batzer R, Liu Y, Cochran DL, Szmuckler-Moncler S, Dean DD, Buyan BD, et al. Prostaglandin mediate the effects of titanium surface roughness on MG63 osteoblast-like cells and alter cell responsiveness to a $\alpha,25\text{-(OH)}_2\text{D}_3$. *J Biomed Mater Res* 1998;41:489–96.
- [129] Overgaard S, Lind M, Glerup H, Bunger C, Soballe K. Porous-coated versus grit-blasted surface texture of hydroxyapatite-coated implants during controlled micromotion: mechanical and histomorphological results. *J Arthroplasty* 1998;13:449–58.
- [130] Wie H, Hero H, Solheim T. Hot isostatic pressing-processed hydroxyapatite-coated titanium implants: light microscopic and scanning electron microscopic investigation. *Int J Oral Maxillofac Implants* 1998;13:837–44.
- [131] Skalak R. Biomechanical considerations in osseointegrated prostheses. *J Prosthetic Dent* 1983;49:843–8.
- [132] Kanth L. The cast (intramobile) screw implant. *DDZ* 1971;25:465–7.
- [133] Brunski JB. *In vivo* bone response to biomechanical loading at the bone/dental–implant interface. *Ad Dent Res* 1999;13:99–119.
- [134] Koch WL. 2-phasic endosseous implantation of intramobile cylindrical implants I. *Quintessence* 1976;27:23–31.
- [135] Kanth L. Titanium plasma coated intramobile conical implants. *ZWR* 1982;91:42–6.
- [136] Kirsch A. The two-phase implantation method using IMZ intramobile cylinder implants. *J Oral Implantol* 1983;11:197–202.
- [137] Gaggl A, Schultes G. Biomechanical properties in titanium implants with integrated maintenance free shock absorbing elements. *Biomaterials* 2001;22:3061–6.

7 Implant-Related Biological Reactions

7.1 Introduction

Dental implants are an ideal option for people in good general oral health who have lost a tooth (or teeth) due to periodontal disease, an injury, or some other reason. Dental implants (as an artificial tooth root and usually made from titanium materials) are biocompatible metal anchors surgically positioned in the jaw bone underneath the gums to support an artificial crown where natural teeth are missing. There are mainly three different types of dental implants: (i) root-form implants, (ii) plate-form implants, and (iii) subperiosteal implants. Using the root-form implants (the closest in shape and size to the natural tooth root), the healing period usually varies from as few as 3 months to 6 or more months. During this time osteointegration occurs. The bone grows in and around the implant creating a strong structural support. Plate-form (or blade-form) implants are usually used when the bone is so narrow that it may not be suitable for the root-form implant, and the area is not suitable for bone grafting. Like root-form implants, there is usually a healing period for osteointegration, although some plate-form implants are designed for immediate restoration (or immediate loading). With very advanced jawbone resorption there may not be enough bone width or height for the root-form or plate-form implant, and the subperiosteal implant may be prescribed. The subperiosteal implant is custom-made and designed to sit on top of the bone, but under the gums.

Generally, any edentulous (toothless) area having enough bone support can be an indication for restoring a missing tooth with an implant. A decision has to be made on a case-by-case basis whether it is a good idea, based on the patient's requirements and expectations. Even though there are practically no absolute contraindications for placement of implants, there are few factors that can put it in a high-risk situation. The following are normally believed to be contraindicative factors: (1) endocrine disorders such as uncontrolled diabetes mellitus, pituitary and adrenal insufficiency, and hypothyroidism can cause considerable healing problems; (2) uncontrolled granulomatous diseases such as tuberculosis and sarcoidosis may also lead to a poor healing response to surgical procedures; (3) patients with cardiovascular diseases or who are taking blood thinning drugs, and patients with uncontrolled hematological disorders such as generalized anemia, hemophilia (Factor VIII deficiency), Factor IX, X, and XII deficiencies, and any other acquired

coagulation disorders are contraindicated for surgical procedures due to poor hemorrhage control; (4) patients with bone diseases such as histiocytosis X, Paget's disease, and fibrous dysplasia may not be good candidates for implants because there is a higher chance for the implant to fail due to poor osteointegration; (5) cigarette smoking; and (6) patients receiving radio and chemotherapy. These groups should not have implants within the 6 months period of therapy [1].

For most patients, the placement of dental implants involves two surgical procedures. *First* (surgical stage), implants are placed within the jawbone. For the first 3–6 months following surgery, the implants integrate with the jawbone—osteointegration (due to successful growing of osteoblasts on and into the rough surfaces of the implant, forming a structural and functional connection between the hard tissue and placed implant). After some months the implant is uncovered and a healing abutment and temporary crown are placed onto the implant. This encourages the gum to grow in the right scalloped shape to approximate natural gums and allows assessment of the final esthetics of the restored tooth. After the implant has integrated/bonded to the jawbone, the *second* (prosthetic) phase begins. The placed implants are uncovered and small posts are attached, which will act as anchors for the artificial teeth. These posts protrude through the gums. When the artificial teeth (or permanent crowns) are placed, these posts will not be seen. The entire procedure usually takes 4–8 months.

There are four major factors influencing the success rates of placed implants. They include (1) correct indication and favorable anatomic conditions (bone and mucosa), (2) good operative technique, (3) patient cooperation (oral hygiene), and (4) adequate superstructure design and fabrication. Failure of a dental implant is usually related to failure to osteointegrate correctly. A dental implant is considered to be a failure if it is lost, mobile, or shows peri-implant bone loss of greater than 1 mm in the first year after postimplanting and greater than 0.2 mm a year after that. Dental implants are not susceptible to dental caries but they can develop a periodontitis condition called peri-implantitis where correct oral hygiene routines have not been followed. Unfortunately, it is true that many times a patient who was evaluated as a good implant patient candidate has a bad history of dental hygiene practice. Failure in dental implants is found to be increased in the anterior mandible where bone quality is not as dense. More rarely, an implant may fail because of poor positioning at the time of surgery, or may be overloaded initially causing failure to integrate. Implant surgery is believed to exhibit its success rate of more than 90% of the time. Occasionally, an implant fails to bond with the surrounding bone. This is usually discovered at the second stage of surgery when the implant is uncovered and the surgeon finds it is loose. In this case, the “failed” implant has to be removed, and another implant can be placed either immediately or later. Potential reasons for implants failing to integrate with surrounding bone include surgical trauma, infection around the implant, smoking (this appears to decrease blood flow to the healing gums and bone, which could interfere with the bonding process), lack of healthy bone (if there is not enough bone for the implant to remain stable, the implant may move around within the bone and bonding will not occur), and titanium allergies (these are extremely rare) [2,3]. Problems also can develop years after implants are placed. For example, just like natural teeth and

gums, the gums around implants can become infected by bacteria, leading to a form of periodontal disease called peri-implantitis. If that situation is left untreated, this condition can cause bone loss, which could cause the implant to become loose and has to be removed. Generally, this situation can be treated using procedures that are very similar to those used to treat periodontal disease affecting natural teeth. Another type of complication that can happen over time is the implant-supported restoration (crown, bridge, or denture) can break or the implant itself can fracture. This usually happens if the occlusion is not aligned properly. If the occlusion is off, too much force (in most cases, torsional or shear force) might be placed on the restoration or implant. Broken restorations often can be repaired, but a fractured implant has to be removed. A broken implant or an implant that fails because of an infection can be replaced with a new implant [1].

On the other hand, orthopedic implants are used to replace damaged or troubled joints. Each implant procedure involves removal of the damaged joint and an artificial prosthesis replacement, including hip, knee, finger, elbow, shoulder, ankle, and trauma products. Orthopedic implants are mainly constructed of titanium alloys for strength and lined with plastic to act as artificial cartilage. Some are cemented into place and others (i.e., cementless) are pressed to fit and allow the patient's bone to grow into the implant for strength. The advantages of orthopedic implants should include an increased mobility, reduced pain, and a higher quality of life. The disadvantages can include a strict postsurgery recovery plan (rehabilitation), infection, and possible malfunction. Each implant is designed to withstand the movement and stress associated with each individual joint and to provide increased mobility and decreased pain. The primary need for orthopedic implants is the result of osteoarthritis, also called degenerative joint disease. When cartilage is worn down, painful bone to bone contact occurs, or cartilage might break down as a result of excess body weight, or the lack of joint movement. Historically, for the domain of the elderly, orthopedic implants are now increasingly used to replace arthritic and/or damaged joints. For hip implants, the form characteristics of the femoral cup and head are critical to its load-bearing capability. Typically, however, the main cause of failure in hip joints is due to wear, and in particular the particles that are generated, resulting in wear debris toxicity. For example, the most common cause of femoral bone loss is due to osteolysis. Although the total cause is not known, it has been attributed to a variety of factors including foreign body reaction to particulate debris, in particular to polymeric debris. As such, the avoidance of wear in hip joints is critical [4].

Today, titanium and some of its alloys are considered to be among the most biocompatible materials. The fact that titanium is being used preferentially in many of the more recent applications in maxillofacial, oral, neurosurgery, and cardiovascular surgery, as well as gaining increasing preference in orthopedics, indicates superiority. Moreover, commercially they have been successfully used for orthopedic and dental implants. Several studies show that when titanium is inserted into human bone it forms an intimate contact with the bone in a process called osteointegration [5–7], due to good biocompatibility, which greatly relies on the formation of stable passive oxide film in a biological system including chemical and mechanical

environments. However, the presence of the passive film is only part of the answer when we consider the complex interfacial phenomena to be found between titanium and a biological system. In this chapter, several important points related to successful implantology will be reviewed.

7.2 Bone Healing

For both dental and orthopedic implant surgeries, bone healing is the most common and major step immediately after implant placements. There is union bone fracture and nonunion bone fracture. For these implant surgeries, it is important to understand the nonunion bone healing mechanism. There are principle steps of peri-implant bone healing. The first and most important healing phase, osteoconduction, relies on the recruitment and migration of osteogenic cells to the implant surface, through the residue of the peri-implant blood clot. This formation of hematoma is similar to that seen elsewhere in the body. This is a clot of blood originating from the lacerated blood vessels in the bone and the periosteum. Among the most important aspects of osteoconduction are the knock-on effects generated at the implant surface by the initiation of platelet activation, which result in directed osteogenic cell migration. Necrotic bone is then resorbed by osteoclasts, and the hematoma by macrophages. As the hematoma is resorbed, granulation tissue develops from the periosteum and endosteum. When this has completed, pluripotent cells migrate into the granulation tissue. These cells become chondrocytes, and later osteocytes, producing cartilage and bone respectively. The second healing phase (bone formation) results in a mineralized interfacial matrix equivalent to that seen in the cement line in natural bone tissue. These two healing phases, osteoconduction and *de novo* bone formation, result in contact osteogenesis and, given an appropriate implant surface, bone bonding. The structure surrounding the fracture site is now slightly harder; this is a provisional callus. The area can be called a proper callus as time goes on, and more and more woven bone is made by the osteoblasts. This woven bone is initially remodeled into lamellar bone. With time, the bone is remodeled over the next few months, and the callus becomes smaller as the trabeculae are formed along lines of stress [8].

A material implanted in bone is always inserted into coagulating blood. Protein and cell interactions during this initial implantation time will govern later healing. Many studies have focused on the tissue surrounding implants. Eriksson et al. [9] developed a method for evaluation of healing around implants in bone by studying cells adhering to the implant surface. Hydrophilic (in other words, active) titanium disks were inserted into rat tibiae. Samples were retrieved after 1, 2, 4, and 8 days of implantation and were analyzed by fluorescence microscopy techniques and scanning electron microscopy (SEM). Both proliferating and apoptotic cells were found on the surface. Generally, cells closest to the implant surface were nonviable, whereas cells in the fibrin network a distance from the surface were viable. Bone morphogenetic protein-2 (BMP-2) is an osteogenic substance. An increase in BMP-2-positive cells was seen during the implantation period, and a population of large

BMP-2—positive cells appeared on the surface after 4 days of implantation. Hence, it was evaluated that this unique method was a suitable tool for rapid evaluation of the initial healing around implant material [9].

Osborn et al. [10] classified bioresponse to endosseous implants into the following three groups: (1) biotolerant type, characterized by distance osteogenesis, (2) bioinert type, characterized by contact osteogenesis, and (3) bioreactive type, characterized by physicochemical linkage between the implant and the surrounding bone. Rutile-type oxide, which is formed on titanium as one of the titanium dioxides, is described as a stable crystalline form similar to ceramics in its bioreactive behavior [11]. However, it is well recognized that Ti is known as a biotolerant biomaterial (which exhibits “distance osteogenesis,” so that although such biomaterials are not rejected from the living tissue, they do not connect to the bone directly because they are covered with connective tissue), and when inserted to the living hard tissue, bone regeneration can be achieved either by bone conductive mechanism (using hydroxyapatite (HA), tricalcium phosphate (TCP), decalcified frozen dried bone, or autologous bone) or bone inductive mechanisms (using BMP on scaffold or platelet-rich plasma (PRP) on scaffold) [12].

Titanium nitride (TiN) has been used in many fields as a coating for surgical instruments, with the purpose of creating materials more resistant to wear and corrosion, and also reducing adhesion. Titanium implants (180 implants with 2 mm × 2 mm) were divided into the following three groups: Group 1 ($n = 60$)—30 machined and 30 machined TiN-coated; Group 2 ($n = 60$)—30 sandblasted and 30 sandblasted TiN-coated; and Group 3 ($n = 60$)—30 titanium plasma sprayed, 30 titanium plasma sprayed and coated with TiN. The animals were killed after 5, 10, 20, 30, or 60 days. It was reported that (i) the healing around the TiN-coated implants was similar to that observed around the uncoated surfaces, and (ii) the TiN coating demonstrated a good biocompatibility, did not have unwanted effects on the peri-implant bone formation [13].

The differences in the healing of cortical and cancellous bone around CpTi screw-type implants with two different surfaces (machined and anodized) were investigated in rabbit tibiae [14]. In the tibiae of rats, a total of 24 implants were surgically placed in randomized arrangement; the upper transverse canal was positioned in the cortical bone region, and the lower transverse canal was positioned in the cancellous bone region. After a 1-month healing period, undecalcified ground sections were subjected to histologic and histomorphometric analyses. It was reported that (i) the percentage of bone-to-implant contact (BIC) inside the upper canals was 16.45% for controls (machined surface) and 24.85% for anodized implants, (ii) BIC inside the lower canals was 7.01% for controls and 11.35% for anodized implants, (iii) the percentage of bone area inside the upper canals was 10.94% for controls and 27.95% for anodized implants, and (iv) the percentage of bone area inside the lower canals was 3.16% for controls and 4.66% for anodized implants. Hence, it was concluded that anodized surface modification of titanium implants is beneficial to both cortical and cancellous bone healing [14].

Franco et al. [15] found similarly the beneficial effect of anodizing the titanium implant surface for bone healing process. The surface of CpTi was treated by

multiphase anodic spark deposition coating to enrich the surface layer with Ca and P ions. Two mongrel dogs received bilateral implantation of three CpTi cylinders in humerus, with anodized and untreated (machined—control). Eight weeks postimplantation, bone fragments containing implants were subject to histologic and histomorphometric analyses. It was reported that (i) in most cases, collagen fiber bundles were detected adjacent and oriented parallel to Ti surfaces, (ii) such connective tissue formation exhibited focal areas of mineralized matrix lined by active osteoblasts, (iii) the mean percentage of BIC were 2.3% for anodized and 0.4% for control implants. It was further concluded that trend of anodizing treated surfaces to support contact osteogenesis in an experimental model that produces low BIC values [15]. Colnot et al. [16], using a mouse model, investigated the effects of implant surface on the early stages of bone healing. The healing around Ti–6Al–4V and other materials was assessed with qualitative cellular and molecular evaluations to show osteoblast differentiation and new bone deposition. Based on results, it was concluded that implant surface and microenvironment around implants favored osteogenesis.

Bone healing is also affected by mechanical environment [17,18]. Ti–7.5Mo (having a high-strength/modulus ratio) can be considered as a candidate for orthopedic applications. Ti–7.5Mo and Ti–6Al–4V implants were placed into the left and right rabbit femurs for 6, 12, and 26 weeks. It was reported that (i) the amount of new bone encircling the Ti–7.5Mo implant was approximately twice that at Ti–6Al–4V by 26 weeks postimplantation, and (ii) this facilitation of bone formation could be associated with unique properties such as a low modulus (less rigidity) and the composition of Mo [17]. During the implant healing, mechanical force is transmitted to osteogenic cells via implant surfaces with various topographies [18]. Rat bone marrow (RBM)—derived osteoblastic cells were cultured on titanium disks with machined and acid-etched surfaces. A loading session consisted of a 3-min application of a 10- or 20- μ m-amplitude vibration. It was found that (i) alkaline phosphatase (ALP) activity and gene expression increased only when the cells were loaded in three sessions/day on machined surfaces, regardless of the vibration amplitude, whereas they were increased with one loading session/day on the acid-etched surface, and (ii) the loading did not affect the osteoblast proliferation on surface, but selectively enhanced the cell spreading on the machined surface. Based on these findings, it was concluded that (i) osteoblastic differentiation is promoted by mechanical stimulation on titanium, and that promotion is disproportionate, depending on the titanium surface topography, and (ii) the frequency of mechanical stimulation, rather than its amplitude, appears to have a crucial role [18].

7.3 Bone Grafting

Bone grafting is performed to unite fractures, to fuse joints, and to repair skeletal defects. There are typically classified into two groups; biograft materials and artificial materials. Biograft materials are further grouped into (i) *autologous grafts*,

which are obtained directly from the patient; autologous bone graft possess maximum biocompatibility thus is generally considered to be the best material available for bone grafting, (ii) *allogeneous grafts*, which are obtained from a donor of the same species and are commonly employed as the “second alternative” when an autograft is not possible; allogeneous bone is also favored when the bone defect is extensive and the quality and quantity of autologous bone is insufficient; the primary problem with allogeneous grafts is immunological, and (iii) *xenogeneous graft*, which is bone material obtained from another species; xenogeneous bone is primarily harvested from cows; these grafts must be specially treated before use because of genetic incompatibility.

The artificial graft materials are also further classified into (i) *natural products* (Paris plaster, coral, etc.) and (ii) *chemical products* which can include sintered HA, β -TCP, self-hardening calcium phosphate (CaP), or others.¹

It is widely recognized that requirements for successful bone regenerating materials should include safety, preservability, handling property, washout resistance, shape plasticity, shape integrity, biocompatibility, and osteoformability (osteoconductivity or osteoinductivity).

7.4 Hemocompatibility

Blood-contacting materials for long-term implantation in the body, such as artificial hearts, artificial valves, and stents, are required to have good blood compatibility. The correlations between Ti oxide layers on oxidized Ti substrates and blood platelet adhesion were examined. Untreated CpTi and three differently treated CpTi (treated in 1–10% hydrogen peroxide for 2–6 h, heated at 300°C, 400°C, and 500°C for 3 h, and treated in 3% H₂O₂ and heated) were tested. It was found that (i) titanium oxide layers formed on Ti by heating displayed less blood platelet adhesion than thin oxide layers on untreated NiTi, (ii) the largest number of adhesive platelets was found on the H₂O₂-oxidized surface, (iii) adhesive platelets could hardly be observed on Ti substrate treated with H₂O₂ and subsequently heated above 300°C, and (iv) the number of blood platelets adhering to these substrates is indicated as follows: H₂O₂-treated CpTi > untreated CpTi > in-air oxidized CpTi > H₂O₂-treated and subsequently oxidized CpTi [19]. Hemocompatibility is a key property of biomaterials that come in contact with blood. Surface modification has shown great potential for improving the hemocompatibility of biomedical materials and devices [19]. The hemocompatibility of the titanium oxide films was characterized in terms of clotting time, blood platelet adhesion and activation, thrombin time, and thrombinogen time. Huang et al. [20] studied the behavior of protein

¹ Allograft—a tissue (bone) graft between individuals of the same species but of nonidentical genetic disposition. Alloplast—a synthetic bone graft materials; a bone graft substitute. Osteogenesis—development of bone; formation of bone. Osteoconduction—process in which the graft acts as a trellis (frame network) or scaffold over which new host bone can form such as HA, β -TCP, or bioglass. Osteoinduction—process in which new bone induced to form through the action of factors contained within the grafted bone, such as proteins or growth factors such as BMP or PRP.

adsorption by irradiation labeling with ^{125}I . Ti–O thin films were prepared by plasma immersion ion implantation (PI³ or PIII) and deposition, and by sputtering. Systematic evaluation of hemocompatibility, including *in vitro* clotting time, thrombin time, prethrombin time, blood platelet adhesion, and *in vivo* implantation into a dog's ventral aorta or right auricle from 17 to 90 days, proved that Ti–O films have excellent hemocompatibility. It is, hence, suggested that the significantly lower interface tension between Ti–O films, blood, and plasma proteins, and the semiconducting nature of Ti–O films, give them their improved hemocompatibility [20].

Already widely used in the orthopedic field as biomaterials, Ti–6Al–4V could be selected as the construction material for blood-contacting devices, such as the left ventricular assist device [21]. Several authors have discussed the biocompatibility and hemocompatibility of pure titanium [22–25]. Protein adsorption studies on titanium oxide, TiO_2 , have been reported [26,27]. Ti–6Al–4V alloy behavior toward bovine serum albumin (BSA) and bovine γ -globulin has been studied using an enzyme-linked immunosorbent assay, and has demonstrated a greater protein binding for Ti–6Al–4V alloy than for stainless steel [28]. These results indicate that the Ti–6Al–4V alloy is well tolerated by blood [21]. It was also suggested that the Ti–6Al–4V alloy is well tolerated by the blood and, therefore, is a promising biocompatible material for construction of biomedical devices, either in the orthopedic field or in the cardiovascular one [21].

Muramatsu et al. [29] evaluated the fibrin deposition and blood platelet adhesion onto alkali- and heat-treated CpTi, alkali- and water-treated CpTi, and alkali- and heat-treated CpTi formed with apatite in simulated body fluid (SBF). They were evaluated by exposure to anticoagulated blood or washed platelet suspension under static conditions and subsequent observation with SEM. It was reported that (i) thrombus formation on alkali-treated CpTi surfaces that were exposed to heparinized whole blood for 1 h was significantly less than that on untreated control CpTi, on which pronounced depositions of fibrin-erythrocytes and lymphocytes were observed, (ii) no thrombus was observed on the apatite-like formed CpTi surface, and (iii) the apatite-like formed CpTi surface exhibits stronger antithrombogenic characteristics than CpTi and other materials examined in heparinized blood [29].

The role of apoptosis/cell death in the inflammatory response at the implanted materials is unexplored. Two surfaces with different cytotoxic potential and *in vivo* outcomes, titanium (Ti) and copper (Cu), were incubated *in vitro* with human monocytes and studied using a method to discriminate between apoptotic and necrotic cells. It was found that Ti surfaces displayed enhanced monocyte survival and production of interleukin-10 (IL-10) and tumor necrosis factor- α (TNF- α). Cu-adherent cells exhibited apoptotic signs as early as 1 h after incubation, but (ii) in contrast to Ti, after 48 h the predominance of apoptotic cells switched to apoptotic/necrotic cells on Cu surfaces, and (iii) material properties rapidly influence the onset of human monocyte apoptosis and progression to late apoptosis/necrosis, concluding that early detection of apoptosis and cell death may be important for the understanding of the biological response to implanted materials [30].

Ion implantation onto NiTi has been used to decrease the surface nickel concentration of this alloy and produce a titanium oxide layer [20]. Nothing is known yet

about the blood compatibility of this surface and the suitability for implants in the blood vessels, like vascular stents. Maitz et al. [31] treated superelastic NiTi by oxygen or helium PI^3 to deplete surface Ni, leading to the formation of a nickel-poor titanium oxide surface with a nanoporous structure. Fibrinogen adsorption and conformation changes, blood platelet adhesion, and contact activation of the blood clotting cascade have been checked as *in vitro* parameters of blood compatibility; metabolic activity and release of cytokines IL-6 and IL-8 from cultured endothelial cells on these surfaces give information about the reaction of the blood vessel wall. It was found that (i) the oxygen-ion-implanted NiTi surface adsorbed less fibrinogen on its surface and activated the contact system less than the untreated nitinol surface, but (ii) conformation changes of fibrinogen were higher on the oxygen-implanted nitinol, (iii) no difference between initial and oxygen-implanted NiTi was found for the platelet adherence, endothelial cell activity, or cytokine release, and (iv) oxygen-ion implantation is seen as a useful method to decrease the nickel concentration in the surface of nitinol for cardiovascular applications [31].

Untreated Ti–6Al–4V and glow-discharge-treated Ti–6Al–4V samples were tested on human peripheral blood mononuclear cells. It was found that (i) apoptosis, undetectable after 24 h of contact with peripheral blood mononuclear cells with the two sample types, is induced after 48 h by treated samples, and, after 48 h, but in the presence of 1.5 $\mu\text{g/mL}$ phytohaemagglutinin (PHA), by both sample types, and (ii) although plasma-treated titanium alloy shows a better biocompatibility in comparison with the untreated one, attention must be paid to the careful control of the first signs of inflammation [32]. Thor et al. [33] investigated the thrombogenic responses of whole blood, PRP and platelet-poor plasma in contact with a highly thrombogenic surface such as titanium. The thrombogenic responses of clinically used surfaces as HA, machined titanium, titania-blasted titanium, and fluoride ion modified grit-blasted titanium were also investigated. It was concluded that (i) whole blood is necessary for sufficient thrombin generation and platelet activation during placement of implants and (ii) a fluoride ion modification seems to segment the thrombogenic properties of titanium [33].

7.5 Cell Adhesion, Adsorption, Spreading, and Proliferation

Ti implant systems have been exploited as bone-anchored implants for many years. Although titanium is well tolerated by the body, the reason for the successful use of this material is not clear. Beneficial effects due to the oxide that spontaneously forms on Ti have been implicated [[34,35], see Chapter 4 for details]. The success is not due to Ti being passively incorporated into the body, since the body recognizes Ti as foreign particles and elicits an inflammatory response. When a biological system encounters an implant, reactions are induced at the implant–tissue interface. Such interfacial reactions include that (1) the body wants to keep the implant isolated, (2) a protective layer of macrophages, monocytes, and giant cells is formed, and (3) a wall of collagen fibers (capsule) is established, and the type of material may influence the fibrous capsule thickness. Surface and interface properties of interest

are chemical composition, contamination and cleanliness, microarchitecture, and structure, etc. [5]. Fibroblasts lay down dense fibrous tissue (collagen, elastin, and reticular) that is gradually replaced by less dense, normal connective tissue, but the body cannot build normal tissue all the way up to an implant.

Host hard/soft tissue response to biomaterials should be considered first as an inflammatory reaction, as mentioned before. Any biomaterial implanted into the body will be perceived as a threat. The host defenses will attempt to eliminate it. This will not happen if the biomaterial is inert and cannot be degraded. Eventually, inert biomaterials will be integrated into the tissue or will become walled off. Biodegradable biomaterials are slowly resorbed over time and are eventually eliminated. Some biomaterials have chemical reactivity and will continue to stimulate over long periods of time. The aforementioned inflammatory processes should include four main stages: initial events (redness, swelling, and pain), cellular invasion (white cells invade tissues), tissue remodeling, repair (being orchestrated by macrophages; occurs differently in different tissues; bone may completely remodel; usually complete within 3–4 weeks), and resolution (extrusion, resorption, integration, and encapsulation). Furthermore, cellular invasion has neutrophil action (main function is phagocytes; die at tissue site; release further inflammatory mediators; prostaglandins, leukotrienes) and macrophages (phagocytes; removal of dead cells; numbers and activity depend on pressure of particulate material). Moreover, resolution is an attempt to return to the original condition: extrusion and resorption of implant material for reestablishment of homeostasis, and integration and encapsulation with a layer of fibrous tissue to establish a steady state [<http://www.medterms.com>; <http://alan.kennedy.name/crohns>].

The response, however, resembles normal wound healing regarding cell recruitment and persistence [36,37]. During the surgical procedure of implantation, the biomaterial most likely will encounter blood. Almost instantly following contact with blood, the implant surface will be covered with plasma proteins that become adsorbed to the surface [38,39]. Ti in contact with serum or plasma is known to adsorb high-molecular weight kininogen, Factor XII, fibrinogen, IgG, prekallikrein, and Clq [40,41]. It was reported that, after 5 s, platelets were found on Ti surfaces exposed to whole blood, while it took about 10 min before polymorphonuclear granulocytes adhered [42]. Protein–platelet [43], leukocyte–platelet [44], and protein–leukocyte [45] are possible interactions at the surface. Furthermore, release of inflammatory mediators at the surface may influence both recruitment and activation of cells [43]. The polymorphonuclear granulocytes are the first leukocytes to be recruited to a Ti surface exposed to blood [42]. Adhesion and activation are two processes polymorphonuclear granulocytes may go through upon material contact. Adhesion involves receptor occupation with appropriate surface ligands [45,46], and when polymorphonuclear granulocytes are challenged with different stimuli, they activate their nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (which are a group of plasma membranes—associated enzymes formed in a variety of cells of mesodermal origin). By using oxygen, the NADPH oxidase produces reactive oxygen species that are used in the cell's defense against microorganisms [43,47].

Close contact between bone and implant has been observed with titanium implants [48–50], but has also been reported with alumina oxide (Al_2O_3) [51] and

zirconium implants [52]. Most authors report a noncellular layer of proteoglycans between bone and titanium [49]. There are indications that implant materials, including a thick proteoglycan layer formation, have a lower biocompatibility than implants producing a thin proteoglycan layer [53,54]. Most of the articles on implant–bone interactions are presented and discussed based on interfacial reaction between metal surface and bone. However, this is not right, since the immediate contacting species of the implant surface is not metal but its oxide. If the implant material is one of titanium materials, titanium oxide should be considered as an extreme surface, contacting the living hard/soft tissue. Titanium reacts immediately with oxygen when exposed to air, forming a very thin surface oxide film. This film, which increases during prolonged exposure to oxygen, consists primarily of titanium dioxide (TiO_2), but Ti_2O_3 and other oxides are also present [55,56]. Ti dioxide has physical/chemical characteristics that differ from metallic Ti, characteristics which are more closely related to ceramics than to metals. As titanium dioxide particles have been used in chromatography, it is well established that titanium oxide surfaces bind cations, particularly polyvalent cations [57]. Titanium dioxide surfaces have a net negative charge at the pH values encountered in animal tissues (around pH 4.0). This binding of cations is based on electrostatic interactions between titanium-linked O^- on the implant surface and cations. The oxide is highly polarized and attracts water and water-soluble molecules in general [54].

The immediate reactions on the implant surface after exposure in the tissues may influence later events, and are conceivably important for the clinical success of the implantation. An understanding of these immediate biological reactions may be significant. The chemical properties of the titanium oxide surface suggest that calcium ions may be attached to the oxide-covered surface by electrostatic interaction with O^- , as just discussed. Calcium deposits have been observed in direct contact with the titanium oxide [53]. According to the same model, calcium-binding macromolecules may adsorb selectively to the implant surface *in vivo* as the next sequence of events. Calcium-binding molecules are often acidic with surface-exposed carboxyl, phosphate, or sulfate groups. Proteoglycans, which contain carboxyl and sulfate groups, might bind to the TiO_2 surface by this mechanism [49,53,54]. HA, the major mineral component of bone, also exhibits a surface dominated by negatively charged oxygen (P-bound) that can attract cations and subsequently anion calcium-binding macromolecules [58,59]. Ellingen [26] treated CpTi surfaces with (1) 100 m mol/L CaCl_2 for 5 min, water washed and air dried, and (2) 100 m mol/L CaCl_2 for 5 min, followed by treating for 24 h with 0.2 mol/L ethylenediaminetetraacetic acid (EDTA), water washed and air dried, with untreated CpTi as a control. The reaction of human serum proteins with TiO_2 was examined and compared with the reaction with HA. It was found that (i) the oxide-covered Ti surfaces reacted with calcium when exposed to CaCl_2 and calcium was identified to a depth of 17 nm into the oxide layer, (ii) surface adsorbed serum proteins were dissolved by EDTA and surfaces of TiO_2 and HA appeared to take up the same selectively from human serum, and (iii) albumin, prealbumin, and IgG were identified by immunoelectrophoresis, suggesting that calcium binding may be one mechanism by which proteins adsorb to TiO_2 , and it is well established that this is the case with HA [26].

During the first week after implantation of Ti in soft tissues, a fluid space, which contains proteins [60] and scattered inflammatory cells [61], separates the implant surface from the tissue. The majority of cells in the fluid space are not in direct contact with the surface during the first week of the healing [62]. However, during later time intervals, macrophages are adherent to the surface of Ti [61,63] and other biomaterials [64]. One factor that may influence the regenerating tissue around the implant is the activity of the macrophages and the release of mediators from macrophages adherent on the implant surface. It is possible that these cells act as “messenger cells,” transmitting information about the implant surface structure and composition to the surrounding tissue [65,66].

Healy and Ducheyne [67] employed surface-sensitive spectroscopies, Auger electron, and X-ray photoelectron spectroscopy (XPS) techniques to characterize changes in Ti oxide composition, oxide stoichiometry, and adsorbed surface species as a function of exposure to human serum in a balanced electrolyte (serum/serum immunoreactive erythropoietin (SIE)), and 8.0 mM EDTA in a balanced electrolyte (EDTA/SIE) at 37 V. It was reported that (i) before immersion, the oxide was near ideal TiO_2 , covered by two types of hydroxyl groups: acidic OH(s) with oxygen doubly coordinated to Ti, and basic Ti-OH groups singly coordinated, and (ii) after extended exposure to both solutions, up to 5000 h (ca. 200 days), the surface concentration of OH groups increased and nonelemental P appeared. The adsorbed phosphate species were presumed to be either $\text{Ti-H}_2\text{PO}_4$ or Ti-HPO^{4-} . Hence, it was suggested that Ti metal is not in direct contact with the biological milieu, but rather there is a gradual transition from the bulk metal, near-stoichiometric oxide, Ca- and P-substituted hydrated oxide, adsorbed lipoproteins and glycolipids, proteoglycans, collagen filaments, and bundles to cells [67]. This finding is very important to develop the gradual functioning implant surface structure, as will be described in Chapter 12.

The protein adsorption behavior of thin films of CaP bioceramic and Ti was investigated by Zeng et al. [68]. The thin films were produced with an ion beam sputter deposition technique using targets of HA, fluorapatite, and Ti. Fourier transform infrared spectroscopy (FTIR) with attenuated total internal reflectance was used to evaluate protein adsorption on these surfaces. It was shown that (i) surface composition and structure influenced the kinetics of protein adsorption and the structure of adsorbed protein, (ii) CaP adsorbed a greater amount of protein than the Ti surface, and caused more alteration of the structure of adsorbed BSA than did the Ti surface, and (iii) the differences in protein adsorption behavior could result in very different initial cellular behavior on CaP bioceramic and Ti implant surfaces [68].

MacDonald et al. [69] surface-modified titanium dioxide particles and investigated their effects on protein adsorption, using a model cell binding protein, human plasma fibronectin (HPF), which is an important matrix glycoprotein that plays a major role in cell and protein attachment. Titanium dioxide surfaces were modified by heating Ti dioxide powder at 800°C for 1 h or treating with an oxidizing agent: peroxide ammonium hydroxide followed by peroxide in hydrochloric acid. Oxidized and control samples were further treated with butanol:water (by 9:1 fraction) for 30 min. It was found that (i) maximum HPF adsorption on modified or unmodified titanium

dioxide occurred within 30 min, with greater protein adsorption occurring on butanol-treated samples, (ii) desorption was minimal with all modifications, and (iii) by modifying the physicochemical properties of titanium dioxide surfaces, it may be possible to alter protein adsorption, and hence optimize cell attachment [69].

The effect of surface roughness (R_a : 0.320, 0.490, and 0.874 μm) of Ti-6Al-4V on the short- and long-term response of human bone marrow cells *in vitro* and on protein adsorption was investigated. Cell attachment, cell proliferation, and differentiation (ALP specific activity) were determined. The protein adsorption of BSA and fibronectin, from single protein solutions on rough and smooth Ti-6Al-4V surfaces was examined with XPS and radiolabeling. It was reported that (i) cell attachment and proliferation were surface roughness sensitive and increased as the roughness of Ti-6Al-4V increased, (ii) human albumin was adsorbed preferentially onto the smooth substratum, and (iii) the rough substratum bound a higher amount of total protein (from culture medium supplied with 15% serum) and fibronectin (10-fold) than did the smooth one [70].

Eriksson et al. [34] treated CpTi surfaces (1) to have a rigid TiO_2 formation by boiling CpTi in $\text{H}_2\text{O}-\text{H}_2\text{O}_2-\text{NH}_4\text{OH}$ (5:1:1) for 5 min, followed by heating at 700°C, or (2) to have a rough (faceted) Ti surface by etching in 10% HF to grow thick oxide film. CpTi surfaces were also treated in concentrated HNO_3 to grow a novel thin oxide, which resulted in a rough surface too. It was observed that all surfaces consisted of TiO_2 covered by a carbonaceous layer. The surfaces were incubated with capillary blood for time periods of between 8 min and 32 h. It was reported that (i) leukocyte adhesion to the surfaces increased during the first hours of blood-material contact and then decreased, (ii) polymorphonuclear granulocytes were the dominating leukocytes on all surfaces, followed by monocytes, (iii) cells adhering to rough surfaces were higher than cells on smooth surfaces, (iv) maximum respiratory burst response occurred earlier on the smooth than on the rough surfaces, and (v) topography had a greater impact than oxide thickness on most cellular reactions investigated, where the latter often had a dampening effect on the responses [36].

Events leading to integration of an implant into bone, and hence determining the long-time performance of the device, take place largely at the interface formed between the tissue and the implant [71]. The development of this interface is complex and is influenced by numerous factors, including surface chemistry and surface topography of the foreign material [35,49,72–74]. For example, Oshida et al. [75] treated NiTi by acid pickling in $\text{HF}:\text{HNO}_3:\text{H}_2\text{O}$ (1:1:5 by volume) at room temperature for 30 s to control the surface topology and selectively dissolve Ni, resulting in a Ti-enriched NiTi surface layer. Zinger et al. [76] investigated the role of surface roughness on the interaction of cells with titanium model surfaces of well-defined topography using human bone-derived cells (MG63 cells) to understand the early phase of interactions through a kinetic morphological analysis of adhesion, spreading, and proliferation of the cells. SEM and double immunofluorescent labeling of vinculin and actin revealed that the cells responded to nanoscale roughness with a higher cell thickness and a delayed apparition of the focal contacts. A singular behavior was observed on nanoporous oxide surfaces, where the cells were more spread and displayed longer and more numerous filopods. On electrochemically microstructured

surfaces, the MG63 cells were able to go inside, adhere, and proliferate in cavities of 30 or 100 μm in diameter, whereas they did not recognize the 10 μm diameter cavities. Cells adopted a three-dimensional shape when attaching inside the 30 μm diameter cavities. It was therefore concluded that nanotopography on surfaces with 30 μm diameter cavities had little effect on cell morphology compared to flat surfaces with the same nanostructure, but cell proliferation exhibited a marked synergistic effect of microscale and nanoscale topography [76].

RBM stromal cells were cultured on either a smooth surface (roughness: 0.14 μm) or a rough surface (5.8 μm) of Ti–6Al–4V disks for 24 or 48 h. Cells on the smooth surface showed typical fibroblastic morphology, whereas cells on the rough surface were in clusters with a more epithelial appearance. RNA was extracted from the cells at both time points, and gene expression was analyzed by using a rat gene microarray. At 24 and 48 h, a similar number of genes were both up- and downregulated at least twofold on the rough surface compared to the smooth surface. It was noticed that (i) roughness did not appear to be a specific stimulator of osteogenesis because genes of both the bone and cartilage lineage were upregulated on the rough surface, and (ii) surface roughness alters the expression of a large number of genes in marrow stromal cells, which are related to multiple pathways of mesenchymal cell differentiation [77]. A highly porous Ti–6Al–4V was fabricated by a polymeric sponge replication method [78]. A polymeric sponge, impregnated with Ti–6Al–4V slurry prepared from Ti–6Al–4V powders and binders, was subjected to drying and pyrolyzing to remove the polymeric sponge and binders. The porous Ti–6Al–4V made by this method had a three-dimensional trabecular porous structure with interconnected pores mainly ranging from 400 to 700 μm and a total porosity of about 90%. The compressive strength was 10.3 ± 3.3 MPa and the elastic constant 0.8 ± 0.3 GPa. It was also reported that MC3T3-E1 cells attached and spread well in the inner surface of pores [78].

The adsorption of BSA onto Ti powder has been studied as a function of protein concentration and pH, and in the presence of calcium and phosphate ions. It was reported that (i) the maximum adsorption at pH 6.8 is 1.13 ± 0.21 mg/m², (ii) for the pH dependence of adsorption, the amount adsorbed increases with decreasing pH (at pH 5.15 the maximum adsorption was 1.31 ± 0.2 mg/m²), indicating that hydration effects are important, and (iii) adsorption increases and decreases in the presence of calcium (at pH 6.8 the maximum adsorption was 1.73 ± 0.23 mg/m²) and phosphate (where at pH 6.8 the maximum adsorption was 0.64 ± 0.14 mg/m²) ions, indicating that electrostatic effects are important [79].

The *in vitro* study was conducted to investigate the adsorption of albumin and fibronectin on titanium surfaces, and the effect of preadsorbed BSA and bovine fibronectin on osteoblast attachment. Maximum adsorption of BSA and fibronectin on Ti surfaces was observed after the incubation for 180 min. In the presence of preadsorbed proteins, osteoblast attachment on Ti surfaces was observed to be enhanced compared to control Ti surfaces. However, cell attachment was affected by the types of protein adsorbed. Preadsorbed albumin was observed to have no significant effect on the amount of osteoblast cells attached. In comparison to the control Ti surface and those preadsorbed with albumin, the Ti surfaces preadsorbed

with fibronectin for 15 min were observed to significantly increase osteoblast cell attachment, whereas the Ti surfaces preadsorbed with fibronectin for 180 min did not affect cell attachment. In addition, cell morphology of the attached cells on protein preadsorbed Ti surfaces was not affected by the type of protein used. Based on these findings, it was concluded that (i) the concentration of fibronectin adsorbed on Ti surfaces was higher compared to albumin, and (ii) the concentration of fibronectin on Ti surfaces plays a role in governing cell attachment [71].

Webster et al. [80] claimed that CaTiO_3 is a strong candidate to form at the interface between HA and titanium implants during many coating procedures. The ability of bone-forming cells (osteoblasts) to adhere on titanium coated with HA, resulting in the formation of CaTiO_3 , was investigated. For formation of CaTiO_3 , titanium was coated on HA disks and annealed either under air or a $\text{N}_2 + \text{H}_2$ environment. Results from cytocompatibility tests revealed increased osteoblast adhesion on materials that contained CaTiO_3 compared to both pure HA and uncoated titanium. The greatest osteoblast adhesion was observed on titanium-coated HA annealed under air conditions. Because adhesion is a crucial prerequisite to the subsequent functions of osteoblasts (such as the deposition of calcium-containing minerals), it was suggested that orthopedic coatings that form CaTiO_3 could increase osteointegration with juxtaposed bone needed to enhance implant efficacy and longevity [80].

Extensive studies on the microstructure, chemical composition, and wettability of thermally and chemically modified Ti–6Al–4V alloy disks were done and correlated with the degree of radiolabeled fibronectin-alloy surface adsorption and subsequent adhesion of osteoblast-like cells [81]. Heating, either in pure oxygen or atmosphere (atm), resulted in an enrichment of Al and V within the surface oxide formed on Ti–6Al–4V [82]. As for the surface contact angle (or wettability), it was reported that (i) preheating (oxygen/atm) or hydrogen peroxide treatment brought a thicker oxide layer with more hydrophilicity when compared with passivated controls, but (ii) posttreatment with butanol resulted in less hydrophilic surfaces than those by heating or hydrogen peroxide treatment. It was therefore indicated that (i) an increase in the absolute content of Al and/or V (heat), and/or in the Al/V ratio (with little change in hydrophilicity; heat + butanol) is correlated with an increase in the fibronectin-promoted adhesion of an osteoblast-like cell line, and (ii) the thermal treatment-induced enhancement of cell adhesion in the presence of the protein is due to its increased biological activity, rather than a mass effect alone, which appear to be associated with changes in chemical composition of the metallic surface [81].

Nanophase materials are unique materials that simulate dimensions of constituent components of bone since they possess particle or grain sizes of less than 100 nm [79], and their interactions with osteoblasts, compared to conventional metals, were studied *in vitro* to synthesize, characterize, and evaluate osteoblast adhesion on nanophase metals (specifically, Ti, Ti–6Al–4V, and Co–Cr–Mo alloys), which are widely used in orthopedic applications. It was found that (i) the osteoblast adhesion on nanophase was more than that on conventional metals, and (ii) nanometal surfaces possessed similar chemistry, and only altered in degree of nanometer surface roughness when compared to their respective conventional counterparts [83].

Improving the biological performance of engineered implants interfacing tissues is a critical issue in implantology and its related science and engineering. Micromotion at the soft tissue–implant interface has been shown to sustain an inflammatory response. To eliminate micromotion, it is desirable to promote cellular and extracellular matrix adhesion to the implant surface. Jain and von Recum [84] modified titanium surfaces topographically or chemically to effect cellular adhesion and to influence cellular interactions and function, and conducted an *in vitro* study to compare the independent effects of surface chemistry and topography on fibroblast-test specimen proximity. Titanium was sputter-coated in stepwise, increasing thicknesses (20–350 nm) onto a series of either smooth or microtextured polyethylene terephthalate (PET), resulting in a stepwise change from a PET surface to a Ti surface—as gradually functioning material. It was found that (i) fibroblast proximity to the coverslip surface increases as the Ti thickness increases on either smooth or textured test specimens, and (ii) fibroblasts were firmly attached to the ridge tops on the coated textured test specimens. Therefore, fibroblast apposition is strongly enhanced by microtextured surfaces and Ti rather than smooth surfaces and PET [84].

Osteoblast adhesion on the implant material surface is essential for the success of any implant in which osseointegration is required. Surface properties of implant material have a critical role in the cell adhesion progress. Zhang et al. [85] employed the microarc oxidizing and hydrothermally synthesizing methods to modify the TiO₂ layer on the titanium surface, on which the mouse osteoblastic cell line (MC3T3-E1) was seeded to evaluate their effect on cell behavior. The surface structure of microarc oxidized samples exhibited micropores with a diameter of 1–3 μm , whereas the microarc oxidation/hydrothermal synthesized samples showed additional multiple crystalline microparticles on the microporous surface. Both treated surfaces possessed higher energy than that of untreated titanium. It was concluded that the microarc oxidation and microarc oxidation/hydrothermal synthesis methods change the surface energy of the TiO₂ layer on the titanium surface, indicating that this may have an influence on the initial cell attachment [85].

Surface characteristics play a vital role in determining the biocompatibility of materials used as bone implants. It is well documented that calcium ion implantation of titanium enhances osteointegration and bone formation *in vivo*. In order to measure the precise effects of ion implantation of titanium on bone cells *in vitro*, alveolar bone cells were seeded on the surface of polished titanium disks implanted with calcium, potassium, and argon ions. Using radioisotopically tagged bone cells, it was found that (i) although the calcium ion implanted surface reduced cell adhesion, it nevertheless significantly enhanced cell spreading and subsequent cell growth, but (ii) in contrast, few differences in bone cell behavior were observed between the potassium- and argon-implanted titanium and the control nonimplanted titanium disks. Based on these findings, it was suggested that the calcium-implanted surface may significantly affect the biocompatibility of titanium implants by enhancing bone cell growth; it was therefore concluded that surface modification by ion implantation could thus prove to be a valuable tool for improving the clinical efficacy of titanium for bone repair and regeneration *in vivo* [86]. Bioactivation of the titanium surface by sodium plasma immersion ion implantation

and deposition (PI^3D) was compared to that of the untreated, Na beam-line implanted and NaOH-treated titanium samples [87]. It was found that (i) from a morphological point of view, cell adherence on the NaOH-treated titanium is the best, (ii) on the other hand, the cell activity and protein production were higher on the nonbioactive surfaces, and (iii) the active surfaces support an osteogenic differentiation of the bone marrow cells at the expense of lower proliferation, due to the high ALP activity per cell [87]. Muhonen et al. [88] investigated the responses of mature osteoclasts cultured on austenite and martensite phases of NiTi shape memory implant material, using the sensitivity of osteoclasts to the underlying substrate and actin ring formation as an indicator of the adequacy of the implant surface. It was reported that osteoclasts tolerated well the austenite phase of NiTi, but the chemically identical martensitic NiTi was not well tolerated by osteoclasts (e.g., indicated by diminished actin ring formation), concluding that certain physical properties specific to the martensitic NiTi have an adverse effect on osteoclast survival in this NiTi phase [88].

Living bone cells are responsive to mechanical loading. Consequently, numerous *in vitro* models have been developed to examine the application of loading to cells. However, not all systems are suitable for the fibrous and porous three-dimensional materials, which are preferable for tissue repair purposes, or for the production of tissue engineering scaffolds. For three-dimensional applications, mechanical loading of cells with either fluid flow systems or hydrodynamic pressure systems has to be considered. The response of osteoblast-like cells to hydrodynamic compression, while growing in a three-dimensional titanium fiber mesh scaffolding material, was evaluated by Walboomers et al. [89]. Bone marrow cells were obtained from the femora of young (12-day-old) or old (1-year-old) rats, and precultured in the presence of dexamethasone and β -glycerophosphate to achieve an osteoblast-like phenotype. Subsequently, cells were seeded onto the titanium mesh scaffolds, and subjected to hydrodynamic pressure, alternating from 0.3 to 5.0 MPa at 1 Hz, at 15-min intervals for a total of 60 min per day for up to 3 days. After pressurization, cell viability was checked. Afterward, DNA levels, ALP activity, and extracellular calcium content were measured. Finally, all specimens were observed with SEM. Cell viability studies indicated that (i) the applied pressure was not harmful to the cells and (ii) the cells were able to detect the compression forces [89].

Improved methods to increase surface hardness of metallic biomedical implants are being developed in an effort to minimize the formation of wear debris particles that cause local pain and inflammation. However, for many implant surface treatments, there is a risk of film delamination due to the mismatch of mechanical properties between the hard surface and the softer underlying metal. Hence, Clem et al. [90] developed a new surface modification of titanium alloy (Ti–6Al–4V), using microwave plasma chemical vapor deposition to induce TiN formation by nitrogen diffusion. The result is a gradual transition from a TiN surface to the bulk titanium alloy, without a sharp interface that could otherwise lead to delamination. The vitronectin adsorption, as well as the adhesion and spreading of human mesenchymal stem cells to plasma-nitrided titanium were evaluated, and they were equivalent to that of Ti–6Al–4V, while hardness is improved three- to fourfold. These

in vitro results suggested that the plasma nitriding technique has the potential to reduce wear, and the resulting debris particle release, of biomedical implants without compromising osseointegration, thus minimizing the possibility of the implant loosening over time [90].

As we have seen above, the biological events occurring at the bone–implant interface are influenced by the topography, chemistry, and wettability of the implant surface. Advincula et al. [91] introduced other method to achieve the aforementioned specific aim. The surface properties of titanium alloy prepared by either surface sol-gel processing, or by passivation with nitric acid, were investigated. The bioreactivity of the substrates was assessed by evaluating MC3T3-E1 osteoblastic cell adhesion, as well as by *in vitro* formation of a mineralized matrix. It was found that (i) surface analysis of sol-gel–derived oxide on Ti–6Al–4V substrates showed a predominantly titanium dioxide (TiO₂) composition with abundant hydroxyl groups, (ii) the surface was highly wettable, rougher, and more porous compared to that of the passivated substrate, and (iii) significantly more cells adhered to the sol-gel–coated surface as compared with passivated surfaces after 1 and 24 h following cell seeding, and a markedly greater number of mineralized nodules were observed on sol-gel coatings [91].

Studies of blood plasma protein interactions with Ti oxides is one possible way to understand blood interactions and tissue integration better, since blood is the first medium encountered after the surgical procedure, and thus governs the subsequent cell attachment and wound healing. Adsorption of albumin and fibrinogen from human blood plasma onto CpTi surfaces with varying oxide properties was studied with an enzyme-linked immunosorbent assay. The intrinsic activation of blood coagulation (contact activation) was studied *in vitro* using a kallikrein-sensitive substrate. It was reported that (i) low fibrinogen and high albumin adsorption was observed for all titanium samples, except for the radio-frequency plasma-treated and water-incubated samples, which adsorbed significantly lower amounts of both and (ii) smooth samples with a surface roughness with less than 1 nm showed some correlation between surface wettability and adsorption of fibrinogen and albumin, whereas rough surfaces (> 5 nm) did not [92]. The role of implant surface topography in cell attachment has been reviewed extensively [5,93–95]. Rough or textured porous surfaces promote cell attachment [96,97]. Surface roughness and composition have been considered the most important parameter for altering cell activity. There are observations that cell responses, such as adhesion, morphology, and collagen synthesis differed on the two grades of CpTi. Between 4 and 24 h, the rate of cell attachment to CpTi (grade I) differed significantly, compared to cell attachment to CpTi (grade IV). At 24 h, the percent of collagen synthesized was significantly more on grade 1 than on grade 4. ALP activity was similar on all substrates. The calcium content was significantly higher on grade 1 than on 4 as well as on glass at 24 h and at 4 weeks. Based on these observations, it was concluded that commonly used CpTi induced differential morphologic and phenotypic changes in human osteoblast-like cells depending on the material grade [98].

Khakbaznejad et al. [99] investigated on osteogenic cells from newborn rat calvariae which were cultured on titanium surfaces, on which cell orientation could be

manipulated, to measure the orientation angles of cells. Substrata included smooth surfaces and smooth regions (gaps) flanked by grooves of 47- μm pitch and 3, 10, or 30 μm depth to create micromachined surfaces. There were several interesting findings reported. Grooves proved effective in orienting cells, but their orienting ability decreased above the ridge level. Cells on the smooth surface showed no preferred orientation. Cells in the gaps became oriented as a result of cell–cell interactions with the cells on the flanking grooves. Cells in the grooves produced oriented collagen fibers, but in the gaps, fibers could be parallel, perpendicular, or diagonal to the grooves. Collagen fibers on the smooth surfaces formed arrays of parallel fibers in a crisscross pattern. In long-term cultures, bone-like nodules were formed, but mostly above the ridge level. Based on these findings, it was reported that grooved surfaces can influence cell orientation both in cell populations above the cells in contact with the grooves and in cell populations adjacent to the grooves [99].

To investigate the roles of composition and characteristics of titanium surface oxides in cellular behavior of osteoblasts, the surface oxides of titanium were modified in composition and topography by anodic oxidation in two kinds of electrolytes; 0.2 M H_3PO_4 , and 0.03 M calcium glycerophosphate + 0.15 M calcium acetate. It was found that (i) calcium and phosphorous ions are incorporated into the anodized surfaces in the form of phosphate and CaP, (ii) the geometry of the micropores in the anodized surfaces varied with diameters up to 0.5 μm in 0.2 M H_3PO_4 , and to 2 μm in 0.03 M Ca–GP and 0.15 M CA, depending on voltages and electrolyte, and (iii) contact angles of all the anodic oxides were in the range of 60–90°, indicating a relative hydrophobicity. As for cell culture studies, the absence of cytotoxicity and an increase of osteoblast adhesion and proliferation by the anodic oxides were found, and cells on the surfaces with micropores showed an irregular, polygonal growth and more lamellipodia [100].

Saldaña et al. [101] evaluated the biocompatibility of the oxidized (700°C $\times$ 1 h and 500°C $\times$ 1 h) surfaces of Ti–6Al–4V by assessing cell adhesion, proliferation, and differentiation of primary cultures of human osteoblastic cells. Compared with polished alloy, both thermal treatments increased osteoblast adhesion measured as cell attachment, $\beta 1$ integrin, and FAK-Y397 expression, as well as cytoskeletal reorganization. It was found that (i) when compared with treatment at 500°C, thermal oxidation at 700°C enhanced cell adhesion, (ii) treatment at 700°C transiently impaired cell proliferation and viability, which were not altered in alloys oxidized at 500°C, (iii) several markers of osteoblastic differentiation such as procollagen I peptide, ALP, osteocalcin, and mineralized nodule formation were found either unaffected or differentially increased by alloys treated either at 500° or 700°C, and (iv) thermal oxidation at 700°C also increased osteoprotegerin secretion. It was therefore concluded that thermal oxidation treatments at 500° or 700°C for 1 h improve the *in vitro* biocompatibility of Ti–6Al–4V [101].

Osteoblast response to Ti implants depends not only on the chemistry of the implant but also on the physical properties of the implant surface, such as microtopography and roughness, as has been reviewed earlier. Early changes in cell morphology and gene expression during the early phase of osteoblast interaction with Ti–6Al–4V surfaces of two different roughnesses were examined. MG63

osteoblast-like cells were cultured for 2, 6, 24, and 72 h on smooth ($R_a = 0.18 \mu\text{m}$) and rough ($R_a = 2.95 \mu\text{m}$) Ti–6Al–4V surfaces. Changes in gene expression for extracellular signal-regulated kinase 2 (Erk2), type I collagen, phospholipase C- γ 2 (Plc- γ 2), and β -actin were measured by reverse transcription polymerase chain reaction (RT-PCR) after 6 and 24 h in culture. It was found that cell number was significantly higher on the smooth surface. Of the genes examined, only Erk2 and β -actin showed a change in expression with surface roughness. Both genes were upregulated on the rough surface at 6 h. Hence, it was indicated that Ti–6Al–4V surface roughness affects osteoblast proliferation, morphology, and gene expression and that these effects can be measured after periods as short as 2–6 h [102].

Stainless steel, CpTi, and Ti–6Al–7Nb are frequently used metals in orthopedic internal fracture fixation. Particularly, clinical uses of Ti–6Al–7Nb are becoming more popular due to its excellent wear resistance. The *in vitro* soft tissue compatibility of Ti–6Al–7Nb in comparison to stainless steel and CpTi, using a human fibroblast model, was conducted by Meredith et al. [103]. It was found that (i) cell morphology and growth rate were similar for stainless steel, electropolished CpTi, and Ti–6Al–7Nb, with cells well spread out and forming a confluent monolayer after 10 days, (ii) cell growth on standard CpTi was similar to the electropolished samples; however, they showed a less spread-out morphology, with more filopodia and surface ruffling present, and (iii) the endocytosis of β -phase particles originating from the standard Ti–6Al–7Nb surface was noted [103].

Polished Ti disks were implanted with high (1×10^{17} ions cm^{-2}), medium (1×10^{16} ions cm^{-2}), and low (1×10^{15} ions cm^{-2}) doses of Ca ions at 40 keV to promote an enhanced osseointegration. The effects of different levels of Ca implantation on morphology, attachment, and spreading of MG63 cells seeded on the surface of the control (nonimplanted) Ti and Ca–Ti disks were examined. The effects of preimmersion of the Ca(high)–Ti in tissue culture medium on cell attachment were measured and correlated with specific chemical changes at the Ti surface. It was reported that (i) although cell adhesion on high-dosed Ca–Ti was initially reduced, it nevertheless was not only restored but substantially increased with progressing culture times, (ii) a significantly enhanced cell spreading, formation of focal adhesion plaques, and expression of integrins were measured on this particular surface, (iii) in contrast, no marked differences were observed in cell behavior on low- and medium-dosed Ca–Ti, (iv) preimmersion studies indicated that the decrease in cell attachment to high-dosed Ca–Ti at early time periods may be linked to the presence of Ca- and P-rich particles on the surface, and (v) the absence of these particles at 24 h was consistent with a significant increase in cell attachment [104].

A Ca-deficient carbonate apatite coating on titanium was prepared by precalcifying titanium in a saturated Ca(OH)₂ solution, and then immersing in a supersaturated CaP solution by Feng et al. [105]. The interaction of the protein with the apatite coating on Ti was investigated by SME with X-ray energy dispersion spectroscopy, XPS, X-ray diffraction, and FTIR. During immersion of the coating in BSA solution, it was observed that calcium and phosphate ions dissolved and reprecipitated, resulting in the formation of the coating contamination BSA from the

surface to subsurface layers. The adsorption modified the structure and morphology of the apatite and changed the protein configuration. It was also found that the protein chemically adsorbed onto surfaces containing calcium or phosphorous, showing that both Ca and P on the apatite coating were the protein-binding sites [105].

Recently, Tetè et al. [106], using SEM and profilometric analysis, investigated the *in vivo* collagen fiber behavior around two different dental implant necks (machined titanium and zirconia implants) in mandibular bone of adult pigs. It was concluded that (i) collagen fiber was similar, regardless of implant material, demonstrating a predominantly parallel or parallel-oblique pattern, and (ii) zirconia, which is used as a transgingival collar on some implants, showed connective tissue adhesion that was similar to that seen on the machined titanium surface, but demonstrated limited plaque formation and may provide better esthetics [106]. The same test combination of titanium and zirconia was studied on the tendency to adhesion and colonization of two periodontal pathogens on both hard surfaces and in soft tissues *in vivo* [107]. The study was designed as a prospective stratified randomized controlled clinical trial. Patients were scheduled to receive two implants with different types of abutments in the posterior mandible. Three months after implant placement, titanium and zirconium abutments were connected. Five weeks after abutment connections, the abutments were removed, probing depth measurements were recorded, and gingival biopsy samples were obtained. Abutments and biopsy specimens were analyzed. It was mentioned that zirconium abutments showed lower surface free energy than titanium abutments. It was further reported that zirconium oxide surfaces have comparable properties to titanium alloy surfaces in their tendency to adhesion and colonization of two periodontal pathogens on both hard surfaces and in soft tissues [107].

Cell adhesion is a fundamental process that controls cell proliferation, migration, and differentiation and is crucial for biomaterial–tissue integration. Osteoblast attachment on the surfaces of implant materials is, therefore, essential for the proper function of any implant in which osteointegration is required. Faghihi et al. [108] investigated the effects of atomic order of specific crystallographic orientation of substrates on cell behavior. It was reported that (i) surface recognition by cells is influenced by the atomic structure of the surface leading to cell-type–specific adhesion (ii) the degree of preosteoblast attachment is significantly higher on the Ti-(1120), whereas the fibroblast adhesion is increased on the Ti-(1010), suggesting that the role of crystal structure in regulating and improving cell–substrate interactions relevant to the optimal function of bone implant materials [108]. Initial attachment of human oral keratinocytes cultured on mirror-surfaced CpTi and yttria-stabilized tetragonal polycrystalline zirconia was investigated [109] and concluded that zirconia has a potential to form epithelial attachment like CpTi.

The cell attachment and gene expression of MC3T3-E1 cells on fibronectin-immobilized titanium was investigated and found that the immobilization of fibronectin on tressylated titanium promoted early matrix mineralization and bone formation [110]. The initial bone cell response to yttria-stabilized zirconia/alumina composite ceramics was studied and compared to CpTi, and found that the zirconia–alumina composite ceramics showed at least equivalent or slightly better biological responses of osteoblast-like cells compared to CpTi during a short-time cell

culture period [111]. The influence of the porous Ti structure on the osteogenic cell behavior was investigated [112]. The porous Ti has the following characteristics: pore size between 50 and 400 μm and a porosity of 60%. Osteogenic cells obtained from human alveolar bone were cultured until subconfluence and subcultured on solid Ti (control) and porous Ti for periods of up to 17 days. It was found that the amount of mineralized matrix was greater on porous Ti compared with the solid one, demonstrating that the porous Ti is an appropriate substrate for osteogenic cell adhesion, proliferation, and production of a mineralized matrix. Shapira et al. [113] studied the behavior of human osteoblast-like cells cultured on Ti–6Al–4V and Ti–6Al–7Nb disks with a rough or a machined surface. It was reported that (i) Ti–6Al–7Nb showed the highest ALP activity, the lowest activity was observed on the machined Ti–6Al–4V surface, and (ii) the highest level of osteocalcin was found in the cells cultured on rough Ti–6Al–7Nb; in addition, higher levels of transforming growth factor were noted for cells cultured on the rough Ti–6Al–7Nb disks, suggesting that the Nb-containing alloy supports more rapid maturation of the osteoblast [113].

7.6 Roughness and Cellular Response to Biomaterials

Eriksson et al. [34] pointed out the importance of surface topography on cellular reactions. Surface plays a crucial role in biological interactions for four reasons. First, the surface of a biomaterial is the only part in contact with the bioenvironment. Second, the surface region of a biomaterial is almost always different in morphology and composition from the bulk. Differences arise from molecular rearrangement, surface reaction, and contamination. Third, for biomaterials that do not release or leak biologically active or toxic substances, the characteristics of the surface govern the biological response. And fourth, some surface properties, such as topography, affect the mechanical stability of the implant–tissue interface [114]. Biomaterials used in a living organism may come into contact with cells in the related tissue for a long period of time. For this reason, they should naturally be harmless to the organism, and their mechanical properties should be suited to the purpose and compatible with receiving tissue surfaces. Furthermore, they should possess a biological effect capable of providing favorable circumstances for the properties and functions of the cells at the implant site. For example, materials used in the construction of an artificial heart or heart valve must provide for antithrombogenesis, which for a dental or bone implant must be suitable for cell attachment, because both the connective and epithelial cells (with which these materials mainly come into contact) are anchorage dependent, and therefore need a cell attachment scaffold for cell division and cell differentiation to be conducted. It is therefore important to investigate attachability of the cells to the materials, which is one of the parameters in the evaluation of biomaterials.

It has been shown that methods of implant surface preparation can significantly affect the resultant properties of the surface and subsequently the biological responses that occur at the surface [115–117]. Recent efforts have shown that the success or failure of dental implants can be related not only to the chemical

properties of the implant surface but also to its micromorphologic nature [118–120]. From an *in vitro* standpoint, the response of cells and tissues at implant interfaces can be affected by surface topography or geometry on a macroscopic basis [118,119], as well as by surface morphology or roughness on a microscopic level [120,121].

Figure 7.1 shows a distribution of surface roughness of implants, which have been clinically used and evaluated as successful implants by the original author (s)'s judgment. It was found that regardless of the type of implant materials used, if the surface roughness is manipulated to have a range from 1 to 50 μm , the implant's survival rate is excellent [122–127]. This finding leads toward a morphological compatibility, which is the third requirement for successful and biofunctional implant systems [128].

These characteristics undoubtedly affect how cells and tissues respond to various types of biomaterials. Of all the cellular responses, it has been suggested that cellular adhesion is considered the most important response necessary for developing a rigid structural and functional integrity at the bone–implant interface [129]. Cellular adhesion alters the entire tissue response to biomaterials [130].

On a macroscopic level (roughness $>10\ \mu\text{m}$), roughness influences the mechanical properties of the titanium–bone interface, the mechanical interlocking of the interface, and the biocompatibility of the material [131,132]. Surface roughness in the range from 10 nm to 10 μm may also influence the interfacial biology, since it is the same order as the size of the cells and large biomolecules [55]. Microroughness at this level includes material defects, such as grain boundaries,

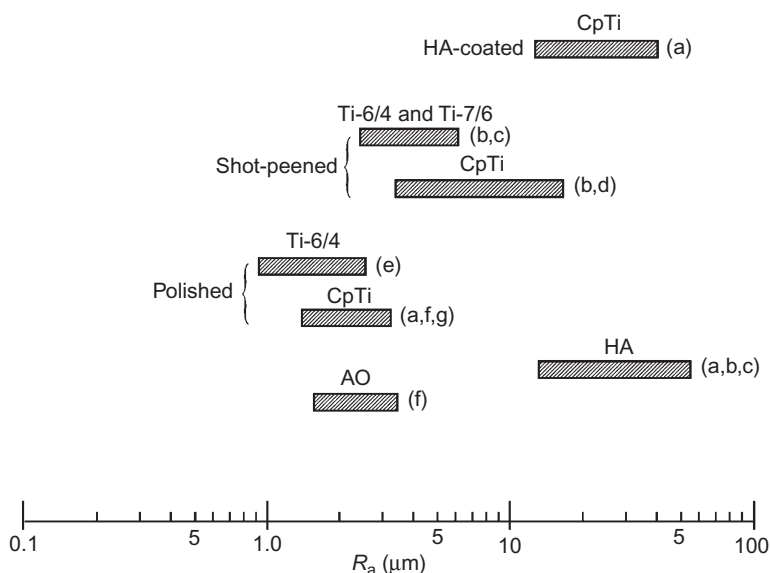


Figure 7.1 Distribution of surface roughness of successfully implanted and clinically biofunctioning materials. a, [119]; b, [122]; c, [123]; d, [124]; e, [125]; f, [126]; and g, [127].

steps and kinks, and vacancies that are active sites for adsorption, and therefore influence the bonding of biomolecules to the implant surface [133]. Microrough surfaces promote significantly better bone apposition than smooth surfaces, resulting in a higher percentage of bone in contact with the implant. Microrough surfaces may influence the mechanical properties of the interface, stress distribution, and bone remodeling [134]. Increased contact area and mechanical interlocking of bone to a microrough surface can decrease stress concentrations resulting in decreased bone resorption. Bone resorption takes place shortly after loading smooth-surfaced implants [135], resulting in a fibrous connective tissue layer, whereas remodeling occurs on rough surfaces [136].

Rich and Harris [120] reported that macrophages exhibited a rugophilia, or an affinity for rough surfaces, whereas fibroblasts failed to readily adhere to these same surfaces. This finding may complement previous work indicating that rough surfaces promote inflammation via macrophage attraction, rather than wound healing by connective tissue [121]. Studies by Brunette [93] and Chehroudi et al. [137,138] have demonstrated that cells of differing organs can orient themselves in the grooves of differing micromachined surfaces. It was determined that epithelial cells were more likely to attach to grooves of specific dimension than to adjacent smooth surfaces. Michaels et al. [139] determined that a higher percentage of osteoblast-like cells attached to rough CpTi surfaces produced by sandblasting than to smoother surfaces polished with 1 μm diamond paste. Keller et al. [140] later confirmed this.

In order to achieve morphological compatibility [128,141], titanium implant surfaces need to be modified. They can be treated by additive methods, such as the titanium beads plasma spray procedure, to increase effective surface area. They have also been modified by subtractive methods such as acid pickling, acid etching, sandblasting, and other small particle blasting to change the texture, as well as to increase the surface area. The development and use of these surface modifications have been based on that an improved osseointegration can be achieved by increasing the topography or roughness of the implant surface [142].

Three types of cylindrical implants (fiber-reinforced composite with porous surfaces, solid polymethylmethacrylate (PMMA), and CpTi) were prepared and inserted in a transverse direction into the intercondylar trabeculae bone area of distal femurs and proximal tibias of New Zealand White rabbits [143]. Histological observation revealed new bone growth into the porous surface of composite implant. Solid PMMA and CpTi implants were encapsulated mostly with fibrous connective tissue. Implanted rough surfaces have long been associated with the accumulation of macrophages and other cells of the monocytic lineage such as foreign body giant cells and osteoclasts [143]. Chehroudi et al. [144] compared events at the interface of implant surface topographies with varied roughness in a rat subcutaneous model. Titanium-casted epoxy replicas were machined, etched, blasted, titanium plasma-sprayed, sandblasted-and-etched, and micromachined, and polished surfaces were implanted for up to 11 weeks. Based on results, it was concluded that there appear to be two routes to bone-like tissue formation on Ti implants in the rat subcutaneous model: macrophage-mediated and macrophage-independent dense collagenous matrix-associated models [144].

7.7 Cell Growth

Titanium implant surfaces with rough microtopography exhibit increased pullout strength *in vivo*, suggesting that the BIC was enhanced. This is supported by *in vitro* studies showing that on surfaces with rough microtopographies, osteoblasts secrete factors that enhance osteoblast differentiation, while decreasing osteoclast formation and activity [145]. A novel approach to electrochemical processing of a HA coating was explored by Hu et al. [146]. Vinyl acetate was added in the electrolytes of calcium and phosphorous in order to improve the adhesion between HA coating and titanium substrate. X-ray powder diffractometer (XRD) spectra indicated that the vinyl acetate did not interfere with the deposition of HA on the surface of titanium cathodes. Results obtained from XPS and SEM revealed that (i) both vinyl acetate and HA were deposited on the titanium cathodes, (ii) the vinyl acetate changed the HA crystalline morphology in the deposition layer, and (iii) the shape and growth direction of the HA crystals in the coating with vinyl acetate differed from those of HA deposition alone. It was moreover mentioned that a preliminary study of the bio-activity showed that osteoblastic cells exhibited higher cell proliferation potential on the HA/vinyl acetate coating than on that of pure HA [146].

Vehof et al. [147] prepared the osteogenic activity of CaP-coated and noncoated porous titanium (Ti) fiber mesh loaded with cultured syngeneic osteogenic cells after prolonged *in situ* culturing to compare in a syngeneic rat ectopic assay model. RBM cells were loaded onto the CaP-coated and noncoated Ti scaffolds using either a droplet or a suspension loading method. After loading, the RBM cells were cultured for 8 days *in vitro*. Thereafter, implants were subcutaneously placed in 39 syngeneic rats. The rats were euthanized and the implants retrieved at 2, 4, and 8 weeks postoperatively. Further, in the 8-week group, fluorochrome bone markers were injected at 2, 4, and 6 weeks. It was reported that (i) histological analysis demonstrated that only the CaP-coated meshes supported bone formation, (ii) the amount of newly formed bone varied, between single and multiple spheres, filling a significant part of the mesh porosity, (iii) in the newly formed bone, osteocytes embedded in a mineralized matrix could be clearly observed, but (iv) on the other hand, in the noncoated titanium implants, abundant deposition of calcium-containing material was seen. In CaP-coated implants, the accumulation sequence of the fluorochrome markers showed that bone formation started on the mesh fibers. It was concluded that the combination of a thin CaP coating, Ti mesh, and RBM cells can generate ectopic bone formation after prolonged *in vitro* culturing [147].

Titanium (Ti) and its alloys continue to serve as successful implant materials for skeletal repair because of their physical properties and biocompatibility. The influence of organoapatite (which is an organic compound in which apatite crystals have been nucleated and grown on a polymer), grown directly onto an L-shaped Ti mesh, on preosteoblastic cellular colonization was investigated. Unseeded mesh samples were placed on subconfluent layers of MC3T3-E1 murine calvaria cells and cultured for up to 2 weeks. It was found that (i) cells demonstrated accelerated colonization of the three-dimensional organoapatite-Ti mesh substrates over bare

Ti controls, (ii) cells also showed significantly increased proliferation on the organoapatite-Ti mesh over bare Ti controls, and (iii) cellular differentiation, measured by ALP and osteocalcin expression, was observed at late stages of the experiment with no notable differences between the organoapatite-Ti mesh and bare Ti controls, suggesting that organoapatite grown onto porous Ti substrates is capable of inducing accelerated colonization of unseeded implant structures by osteogenic cells [148].

Rodriguez et al. [149] modified titanium surfaces by anodization in a mixed electrolyte of calcium glycerophosphate and calcium acetate. Hydrothermal treatments were performed on two of the anodized groups for either 2 or 4 h. *In vitro* osteoblast response to anodized oxide and the hydrothermal-treated oxide after anodization was evaluated. It was found that (i) calcium and phosphorus ions were deposited on the Ti oxide during anodization, (ii) anodized surfaces following a 4-h hydrothermal treatment were observed to promote the growth of apatite-like crystals, as compared with anodized surfaces after a 2-h hydrothermal treatment, (iii) cellular function and onset of mineralization, as indicated by protein production and osteocalcin production, respectively, were also observed as enhanced on hydrothermal-treated surfaces. It was thus concluded that CaP and apatite-like crystals could be deposited on Ti surfaces using anodization and a combination of anodization and hydrothermal treatment, and the phenotypic expression of an osteoblast was enhanced by the presence of CaP or apatite-like crystals on anodized or hydrothermally treated Ti surfaces [149].

The topographic effects of HA and titanium (Ti) surfaces having identical micropatterns were determined as to whether there was synergistic interaction between surface chemistry and surface topography. Surface microgrooves with six different groove widths (4, 8, 16, 24, 30, and 38 μm) and three different groove depths (2, 4, and 10 μm) were made on single crystalline silicon wafers using microfabrication techniques. Ti and HA thin films were coated on the microgrooves by radio-frequency magnetron sputtering, followed by seeding human osteoblast-like cells and culturing on the microgrooved surfaces for up to 7 days. It was reported that (i) contact guidance and cell shape changes were observed on the HA and Ti microgrooves, and (ii) no difference in orientation angle between HA and Ti microgrooves was found, suggesting that surface chemistry was not a significant influence on cell guidance [150].

The homogeneous deposition of CaP can be coated on porous implants by immersion in simulated physiologic solution. In addition, various CaP phases, such as octacalcium phosphate or bone-like carbonated apatite, can be applied. Barrère et al. [151] conducted experiments (1) to investigate the osteoinduction of octacalcium phosphate-coated and noncoated porous tantalum cylinders, and of dense titanium alloy cylinders (5 mm in diameter and 10 mm in length) in the back muscle of goats at 12 and 24 weeks and (2) to compare the osteogenic potentials of bone-like carbonated apatite-coated, octacalcium phosphate-coated, and bare porous tantalum cylinders in a gap of 1 mm created in the femoral condyle of a goat at 12 weeks. It was found that (i) in the goat muscle, after 12 weeks, the octacalcium phosphate-coated porous cylinder had induced ectopic bone, as well as bone within

the cavity of the octacalcium phosphate-coated dense titanium cylinder, (ii) in the femoral condyle, bone did not fill the gap in any of the porous implants, but (iii) in contrast with the two other groups, octacalcium phosphate-coated porous cylinders exhibited bone formation in the center of the implant [151].

Studies examining osteoblast response to controlled surface chemistries indicate that hydrophilic surfaces are osteogenic. The TiO_2 surfaces, however, produced until now exhibit low surface energy because of adsorbed hydrocarbons and carbonates from the ambient atmosphere, or roughness induced hydrophobicity. Zhao et al. [152] used hydroxylated/hydrated Ti surfaces in order to retain high surface energy of TiO_2 . It was reported that (i) osteoblasts grown on this modified surface exhibited a more differentiated phenotype, characterized by increased ALP activity and osteocalcin, and generated an osteogenic microenvironment through higher production of prostaglandin E2 (PGE2) and TGF- β 1, and (ii) 1α , 25(OH)2D3 increased these effects in a manner that was synergistic with high surface energy, suggesting that increased bone formation observed on modified Ti surfaces *in vivo* was due in part to stimulatory effects of high surface energy on osteoblasts [152].

To further understand the biological mechanisms underlying bone–titanium integration and biomechanical properties of the integrated bone, Takeuchi et al. [153] cultured RBM-derived osteoblastic cells on either the machined titanium disk or acid-etched titanium disk. It was found that (i) the modulus of elasticity (MOE) of the mineralized tissue was also three times greater on the acid-etched surface than on the machined surface, and (ii) after 28 days of culture, the mineralized nodule area was significantly lower on the acid-etched surface than on the machined surface, while total calcium deposition did not differ between the two surfaces, indicating denser mineral deposition on the acid-etched surface. SEM images revealed that tissue cultured on the acid-etched titanium exhibited plate-like, compact surface morphology, while the tissue on the machined titanium appeared porous and was covered by fibrous and punctate structures. It was therefore concluded that culturing osteoblasts on rougher titanium surfaces enhances the hardness and elastic modulus of the mineralized tissue associated with the condensed mineralization, accelerated collagen synthesis, and upregulated expression of selected bone-related genes [153]. An electrochemical anodization treatment was used to produce a network oxide layer on Ti surface. Human bone marrow mesenchymal stem cells were made to express green fluorescent protein. The green fluorescent protein signal was measured *in situ* to assess cell growth on Ti surfaces. It was found that the formation of TiO_2 nanonetwork on the Ti surfaces can increase the human bone marrow mesenchymal stem cell growth *in vitro* and *in vivo* [154].

7.8 Tissue Reaction and Bone Ingrowth

The oral epithelium and connective tissue was able to form a peri-implant epithelium similar in appearance to that around natural teeth [118,155]. In studies of peri-implant mucosa conducted in 9-month-old beagle dogs, placement of one-stage and two-stage implants demonstrated that the mucosal barrier that formed had a definite

epithelial, and the connective tissue component was similar in dimension in both the one-stage and two-stage implants [156]. It was proposed that a certain minimum width of the peri-implant mucosa was required, and that bone resorption would occur if the soft tissue dimension was not satisfied, being similar to the phenomenon of the biologic width that occurs in natural human dentition [157]. The connective tissue lateral to the junctional epithelium is comprised of dense collagenous tissue with few vascular structures and scattered inflammatory cells. The “zone of connective tissue integration” between the bone crest and the junctional epithelium is characterized as a collagen-rich and cell-poor scar-like connective tissue. There was a narrow zone close to the implant that had mainly collagen fibers running parallel to the surface of the implant and attaching to the periosteum of the bone [156]. Using light microscopy, it was noted that the inner peri-implant epithelium ended 1–2 mm from the bone [158]. Using transmission electron microscopic studies, it was noted that the outermost epithelial cells close to the implant exhibited condensed structures resembling hemidesmosomes [159]. Good adhesion between the implant surface and the soft tissue is extremely important to assure the survival of dental implants [160]. Percutaneous and permucosal implants require a strong support from the underlying connective tissue if an epithelial downgrowth and subsequent failure are to be avoided [161]. Systematic and continuous monitoring of peri-implant tissues during maintenance care is recommended for the early diagnosis of peri-implant disease [93,162]. Tissue reaction has been shown to vary with micrometer range changes in the substratum [163]. Studies have shown that changes in the range of 130 nm are adequate to produce changes in contact guidance of the cells [164]. Surface roughness may have had a significant effect on the cell density and proliferation. Some studies concluded that surface microtexture influences the attachment and growth of human gingival fibroblasts [165,166], while others suggested that the surface roughness does not influence soft tissue attachment [167]. Significantly, greater numbers of cells were attached to rougher milled and sintered surfaces than to polished surfaces, possibly indicating higher proliferation capacity [168].

The distribution of released metal in the surrounding tissue is important information to estimate the relation between the dissolution content and tissue response. However, the distributions of released metal have not been studied well because of the difficulty in detecting the very low concentration of rarely contained metal elements in the surrounding tissue. Soft tissues implanted with Cu, Ni, Fe, Ag, Ti, NiTi, 304 (18Cr–8Ni) and 316 (18Cr–8Ni–2Mo) stainless steel wires were investigated with X-ray scanning analytical microscope (XSAM) and compared with histological observation. The relationship between the distribution metal elements and the tissue response was evaluated. Severe damage was observed around Ni and Cu implants, while fibrous connective tissue was formed around the Fe implant. The dissolved concentration was approximately 10–20 mM for Ni and Cu, and was considered to be on the order of 10 times higher in Fe. It was concluded that (i) the toxicity at the same concentration followed the sequence (from greater toxicity to least): Ni > Cu > Fe and (ii) for Ag, Ti, NiTi, 304, and 316 stainless steel implants, significant dissolution and severe tissue damage were not observed [169].

Sundgren et al. [170] used Auger electron spectroscopy to study the interface between human tissue and implants of Ti and stainless steel. Both the thickness and the nature of the oxide layers on the implant have been found to change during the time of implantation. The stainless steel implants have a surface oxide about 50 Å thick prior to implantation. The metal atoms in the oxide are mainly Cr, with which Cr_2O_3 may be formed. For implants located in cortical bone, the thickness of the interfacial oxide layer remains unaffected, while it increases by a factor of 3–4 on samples located in bone marrow. In both these cases, Ca and P are incorporated in the oxides. Implants located in soft tissue have an interfacial oxide with a thickness of about one and a half times that of an unimplanted sample. On these samples, Ca and P are not incorporated in the oxide layer. Also, for Ti an increase in oxide thickness and an incorporation of Ca and P are found. In the cases with Ti implants, it is also demonstrated that the oxidation process occurs over a long period of time, up to several years. For the elements incorporated in these interfacial oxide layers on both stainless steel and Ti implants, it is found that P is strongly bound to oxygen, suggesting the presence of phosphate groups in the oxide. Other species that can oxidize the implants are H_2O_2 and free radicals, such as O_2^- or OH^- . Such species are normally produced during the inflammatory reactions [[170], Chapter 4].

The immuno-inflammatory responses to stainless steel (21 implants in 20 patients) and Ti plates (22 implants in 20 patients) used in the treatment of long bone fractures were studied. All fractures healed without complications. It was reported that (i) in the soft tissue adjacent to the surface of the implants, a dark discoloration of the tissue was visible in 18 out of 21 stainless steel implants and 20 out of 22 Ti plates, and (ii) tissue specimens of all patients contained positive staining for macrophages (CD68-positive cells), demonstrating clearly the presence of a marked inflammation and tissue reaction in the soft tissue covering stainless steel and Ti plates that were used for internal fixation of bones, independently from the material [171].

Successful clinical performance of machine/turned CpTi implants has resulted in a widespread usage of them. However, in bone of poor quality and quantity, the results have not always been so good, motivating the development of “novel types of osseointegrated implants.” The development of Ti implants has depended on new surface processing technologies. Recently developed clinical oral implants have been focused on topographical changes of implant surfaces, rather than alterations of chemical properties [172–176, and see Figure 7.1]. These attempts may have been based on the concept that mechanical interlocking between tissue and implant materials relies on surface irregularities in the nanometer to micrometer level. Recently, published *in vivo* investigations have shown significantly improved bone tissue reactions by modification of the surface oxide properties of Ti implants [177–183]. It was found that in animal studies, bone tissue reactions were strongly reinforced with oxidized titanium implants, characterized by a titanium oxide layer thicker than 600 nm, a porous surface structure, and an anatase type of Ti oxide with large surface roughness compared with turned implants [182–184]. This was later supported by work done by Lim et al. [185], who found that the alkali-treated

CpTi surface was covered mainly with anatase type TiO_2 , and exhibited hydrophilicity, whereas the acid-treated CpTi was covered with rutile-type TiO_2 with hydrophobicity. Besides this characteristic crystalline structure of TiO_2 , it was mentioned that good osseointegration, bony apposition, and cell attachment of Ti implant systems [186,187] are partially due to the fact that the oxide layer, with unusually high dielectric constant of 50–117, depending on the TiO_2 concentration, may be the responsible feature [55,188].

Turned (as-machined implants) with amorphous TiO_2 , anatase TiO_2 with S, amorphous TiO_2 with P, and anatase TiO_2 with Ca were prepared by the microarc oxidation method. Eighty implants were inserted in the femora and tibiae of 10 mature New Zealand White rabbits for 6 weeks. It was reported that (i) the removal torque values showed significant differences between S implants and controls, Ca implants and controls, Ca implants and P implants but did not show significant differences between the others, and (ii) the bone to metal contact around the entire implants demonstrated a 186% increase in S implants, 232% increase in P implants, and 272% increase in Ca implants when compared to the paired control groups. It was therefore concluded that surface chemistry and topography separately or together play important roles in bone response to the oxidized implants [176].

The effects of pure commercial titanium implants on the process of primary mineralization was studied by Kohavi et al. [189] by insertion of titanium implants into rat tibial bone after ablation. The effects of the titanium were studied through the behavior of extracellular matrix vesicles. It was found that the insertion of titanium implants was followed by an increase in the number of extracellular matrix vesicles, as well as vesicular diameter, and by a decrease in vesicular distance from the calcified front when compared to normal healing. It was therefore suggested that (i) the process of extracellular matrix vesicles maturation around titanium implants was delayed when compared to normal primary bone formation during bone healing, and (ii) the delay in mineralization was compensated by an increase in vesicle production, resulting in an enhancement of primary mineralization by the titanium [189].

Jasty et al. [190] investigated bone ingrowth into uncemented hemispherical canine acetabular components, porous-coated with Co–Cr spheres and compared them to those porous-coated with titanium fiber mesh. Good bone ingrowth was noted in both types of porous coatings at 6 weeks after surgery, with no difference in the histologic quality of the ingrowth bone. Quantification of bone ingrowth showed that significantly more bone grew into the titanium fiber mesh porous-coated components. It was demonstrated that the mean values of the amount of bone ingrowth, the area density of the ingrowth bone inside the pores, the ingrowth bone penetration depth, and the degree of the periphery of the porous layer with bone ingrowth of titanium mesh exceeded those values with Co–Cr spheres [190].

Bony ingrowth to control (nontreated) and heat-treated 316L stainless steel and Ti–6Al–4V implants, which were placed into the medullary canal of the femur in rats, was studied by mechanical, chemical, and Auger electron spectroscopic microanalysis. Control samples of both materials are autoclaved at 280°C. Heat treatment was done at 550°C for 1.5 h. It was found that, at all time intervals up to 35 days postimplantation, the shear strengths of the heat-treated Ti–6Al–4V and stainless

steel implants were significantly higher (1.6- to 3.4-fold) than in control implants. Using Auger electron spectroscopy depth profiling methods, it was also found that the heat treatment modified the implant surface composition significantly, resulting in a thicker oxide layer and other chemical changes. It is therefore concluded that preoxidation of metallic implants prior to their insertion alters their chemical surface property and augments bony ingrowth to them [191].

Interstitial bone ingrowth is extremely important for optimum fixation of implanted materials under load-bearing conditions. Three types of biomaterial test pieces were manufactured in solid and open-pore structures and implanted into dog femoral condyles. Bone formation and remodeling were observed histologically and roentgenologically for 24 weeks thereafter. It was reported that (i) at 24-week postimplantation, thick fibrous tissue surrounded by corticalized bone was formed around both solid smooth-surfaced alumina and titanium implants, (ii) on the other hand, with an implant made of an artificial osteochondral composite material, thickening of ingrowth trabeculae could be observed as early as 4 weeks, (iii) bone ingrowth into the titanium fiber mesh was abundant and increased with time after implantation. This interstitial bone ingrowth resulted in the complete integration of the implant and the viable host bone. It was thus suggested that interstitial bone ingrowth has great significance; even new bone formation and remodeling follows Wolff's law [<http://www.teambone.com/wolff.html>] after the completion of the bonding between the bone and implanted material under load-bearing conditions. The artificial osteochondral composite material could lead to complete integration of the implant and viable bone, suggesting that it is a promising material for joint replacements. Moreover, the tibial joint surface, which bore against the polyvinyl alcohol hydrogel surface of this implant, remained intact, suggesting that this composite is a very promising biomaterial for use in joint prostheses [192].

The histological study was conducted on the surrounding tissues of two screw-shaped titanium plasma-sprayed implants, retrieved due to the fractured abutment after 18 and 42 months. The microscopical examination showed that a large part of the implant surface on both implants was covered by compact, mature lamellar bone, with the presence of many Haversian systems and osteons. With von Kossa staining at the interface with the implant, the bone was highly mineralized, and any connective tissue or inflammatory cells were not present at the interface [193].

The micromotion chamber for implantation in the rabbit tibia consists of two titanium components that have a 1 mm continuous (not independent) pore for bone ingrowth. The fixed, outer cylinder of the chamber contains a movable inner core that can be manually rotated. A comparison was made between the histological and scintigraphic results of bone ingrowth into chambers having a congruently shaped interface that was moved at 20 cycles/d, with amplitude of either 0.5 or 0.75 mm. It was found that (i) histological sections from both amplitude groups contained extensive new woven and trabecular bone, embedded in a fibrovascular network; however, (ii) the chambers with a larger amplitude of motion yielded less bone ingrowth than those with a smaller amplitude. It was therefore suggested that short, discrete periods of motion can stimulate the formation of fibrous tissue rather than bone, using the parameters chosen in this model [194].

Li et al. [195] investigated the effect of the surface macrostructure of a dimpled CpTi implant on bone ingrowth *in vivo* by means of histological examination and a push-out test. Cylindrical implants were inserted in one femur of each experimental rabbit, and the animals were killed at 1.5, 3, and 13 months after implantation. The femur with the implant of each animal was then examined in a push-out test. The fracture surfaces of the bone–implant interface were examined after the push-out test under light and electron microscopy. It was reported that the dimpled CpTi surface enhanced mechanical retention of the CpTi implant in bone due to interlocking between vital bone and the dimples [195].

A nonsubmerged ITI-Bonefit implant, after a loading period of 4 years, was examined. It was reported that the behavior of peri-implant bone was tightly related to the magnitude and concentration of stresses which were transmitted to the implant [196]. These peri-implant stresses are subject to several variables: opposing occlusion, bite force, number of implants available to carry the load, position of the implant within the prosthesis, rigidity of the prosthesis, and implant geometry [196]. Moreover, torque or bending moments can be applied to implants, for example, by excessively cantilevered bridges, and can produce a breakdown at the interface, a resorption of bone, a loosening of the screw, and/or a fracture of the bar/bridge [197]. It is also significant that the fracture was associated with a severe and rapid marginal bone height loss, and with an almost 100% bone–implant contact [198].

The *in vivo* effect of biomimetic CaP coating of titanium implants on peri-implant bone formation and bone–implant contact was investigated by Schliephake et al. [199]. Five types of implants were used: Ti–6Al–4V implants with a polished surface; Ti–6Al–4V implants with collagen coating; Ti–6Al–4V implants with a mineralized collagen layer; Ti–6Al–4V implants with a sequential coating of HA and collagen; and Ti–6Al–4V implants with HA coating only. All implants were press-fit inserted into 4.6 mm trephine burr holes in the mandibles of 10 beagle dogs. The implants of five animals each were evaluated after a healing period of 1 month and 3 months, respectively, during which time sequential fluorochrome labeling of bone formation had been performed. Bone formation was evaluated by morphometric measurement of the newly formed bone around the implants and the percentage of implant bone contact. It was reported that (i) after 1 month, there was a significantly higher percentage of mean bone–implant contact in the HA-coated implants compared to those with polished surfaces and those with the collagen-coated surface, but (ii) after 3 months, these differences were not present anymore, and (iii) bone apposition was significantly higher next to implants with sequential HA/collagen coating compared to the polished surfaces and mineralized collagen layer. It is concluded that the HA coating to titanium implants has increased bone–implant contact in the early ingrowth period, and the addition of collagen to a HA coating layer may hold some promise when used as a sequential HA/collagen coating with mineralized collagen as the surface layer [199].

A major consideration in designing dental implants is the creation of a surface that provides strong attachment between the implant and bone, connective tissue, or epithelium. In addition, to maintain plaque-free implants, it is important to inhibit the adherence of oral bacteria on titanium surfaces exposed to the oral

cavity. Therefore, Groessner-Schreiber et al. [200] examined antimicrobial characteristic TiN. Mouse fibroblasts were cultured on smooth titanium disks that were either magnetron-sputtered with a thin layer of TiN or thermal oxidized, or modified with laser radiation (using a Nd:YAG laser). It was reported that (i) fibroblasts on oxidized titanium surfaces showed a more spherical shape, whereas cells on laser-treated titanium and on TiN appeared intimately adherent to the surface, and (ii) when compared to all other surface modifications, fibroblast metabolism activity and total protein were significantly increased in the fibroblasts cultured on titanium surfaces coated with TiN, suggesting that a TiN coating might be suitable to support tissue growth on implant surfaces [200].

Osteoconductive apatite coatings represent an established technology for enhancing the integration of orthopedic Ti implants with living bone. The *in vivo* evaluation of a biomimetic apatite coating was performed. A dense and substantially pure ceramic coating with a crystal size of less than 1 μm was fabricated by using a mixed solution including all major inorganic ions (Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Cl^- , HPO_4^{2-} , HCO_3^- , and SO_4^{2-}). The biomimetic apatite coating was grown on Ti-6Al-4V at 45°C for 4 days. Three types of measurements were taken on linear ingrowth percentage, area ingrowth percentage, and continuous bone apposition percentage. It was demonstrated that (i) under controlled conditions, the apatite coating appears to resorb in 8 weeks, and stimulated early osseointegration with the metal surface with a reduction in fibrous tissue encapsulation, and (ii) this coating may, therefore, be useful in facilitating early bone ingrowth into porous surfaces without the potential for coating debris, macrophage infiltration, fibrous tissue encapsulation, and eventual coating failure, as may occur with current plasma-sprayed HA-coating techniques [201].

Roughened titanium surfaces have been favorably fabricated and widely used for dental implants, as has been seen above. In recent years, there has been the tendency to replace Ti plasma-sprayed surfaces with sandblasted and acid-etched surfaces in order to enhance osseous apposition. Another approach has been the utilization of HA-coated implants. Knabe et al. [202] examined the effect of two roughened Ti dental implant surfaces on the osteoblastic phenotype of human bone-derived cells, and compared this behavior to that for cells on a HA-coated surface. Test materials were an acid-etched and sandblasted Ti surface, a porous Ti plasma-sprayed coating, and a plasma-sprayed porous HA coating (HA). Smooth Ti-machined surfaces served as the control. Human bone-derived cells were grown on the substrata for 3, 7, 14, and 21 days, counted and probed for various bone-related mRNAs and proteins (type I collagen, osteocalcin, osteopontin, osteonectin, ALP, and bone sialoprotein). It was reported that (i) dental implant surfaces significantly affected cellular growth and the temporal expression of an array of bone-related genes and proteins, (ii) HA-coated Ti had the most effect on osteoblastic differentiation, inducing a greater expression of an array of osteogenic markers than recorded for cells grown on acid-etched and sandblasted Ti and porous Ti plasma-sprayed Ti, thus suggesting that the HA-coated surface may possess a higher potency to enhance osteogenesis, and (iii) acid-etched and sandblasted Ti surfaces induced greater osteoblast proliferation and differentiation than porous Ti plasma-sprayed Ti [202].

Lu et al. [203] evaluated the osteoconduction of Ti–6Al–4V surfaces under various conditions, including micropatterned, alkali-treated, micropatterned plus alkali-treated, and surfaces without any treatment as the control. The *in vitro* CaP formation on titanium surfaces was in static and dynamic SBF. An *in vivo* comparison was conducted in the medullary cavity of a dog femur, which could provide the same physiological environment for specimens with different surface conditions. It was reported that (i) there was good conduction of CaP on the alkali-treated surfaces, and also better CaP deposition on the microhole surface than on the flat surfaces in the dynamic SBF was found, and (ii) the beneficial effect of alkaline treatment on osteoconduction was confirmed. The *in vivo* experiments also indicate a synergistic effect of the alkaline treatment and the topographic pattern on osteoconduction [203], as suggested by basic studies done by Lim et al. [185].

Early bone ongrowth is known to increase primary implant fixation and reduce the risk of early implant failure. Arg–Gly–Asp (arginine–glycine–aspartate, RGD) peptide has been identified as playing a key role in osteoblast adhesion and proliferation on various surfaces. Elmengaard et al. [204,205] evaluated the effect of RGD peptide coating on the bony fixation of orthopedic implants. Sixteen unloaded cylindrical plasma-sprayed Ti–6Al–4V implants, coated with cyclic RGD peptide, were press-fit inserted in the proximal tibia of eight mongrel dogs for 4 weeks. Uncoated control implants were inserted in the contralateral tibia. Results were evaluated by histomorphometry and mechanical push-out tests. It was shown that (i) a significant twofold increase was observed in bone ongrowth for the RGD-coated implants, (ii) fibrous tissue ongrowth was significantly reduced for the RGD-coated implants, (iii) bone volume was significantly increased in a 0–100 μm zone around the implant; the increased bony anchorage resulted in moderate increases in mechanical fixation, as the apparent shear stiffness was significantly higher for RGD-coated implants, and (iv) increases in median ultimate shear strength and energy to failure were also observed. It was hence suggested that cyclic RGD coating increases early bony fixation of unloaded press-fit titanium implants [204,205].

It has been extensively discussed about interfacial reaction of placed implant with hard tissue, but its reaction with soft tissue should be equally important. Tissues containing Ti dental implants were examined on the chemical state of Ti transferred from the placed implant into surrounding soft tissue [206]. No tissues that contacted CpTi cover screws for several months were excised in a second surgery whereby healing abutments were set. Six tissues that surrounded implants retrieved due to their failure were also exercised. It was concluded that (i) the existence of Ti in the tissue did not cause implant failure. Intraosseous transcutaneous amputation prostheses reply on the integrity of soft tissue–implant interface as a barrier to exogenous agents, and the prevention of avulsion and marsupilization [206]. Chen et al. [207] had conducted *in vivo* evaluation of soft tissue attachment to Ti–6Al–4V transcutaneous custom-made screws treated by a microarc oxidation method. The experimental model comprised implantation of 16 transcutaneous screws in the medial aspect of the left tibia of eight female goats. It was reported that (i) significant higher soft tissue attachment was observed in the microarc oxidized Ti–6Al–4V alloy group compared to the control and (ii) the *in vivo* data

indicated that modified Ti–6Al–4V alloy could be a useful biomaterial for tissue engineering and benefit applications where bone-anchored transcutaneous implants are used [207].

7.9 Osteointegration and Bone–Implant Interface

Broadly speaking, two types of anchorage mechanisms have been described: biomechanical and biochemical. Biomechanical binding is when bone ingrowth occurs into micrometer-sized surface irregularities. The term osteointegration is probably, realistically, the biomechanical phenomenon. Biochemical bonding may occur with certain bioactive materials where there is primarily a chemical bonding, with possible supplemental biomechanical interlocking. The distinct advantage with the biochemical bonding is that the anchorage is accomplished within a relatively short period of time, while biomechanical anchorage takes weeks to develop. This would clinically translate into the possibility of earlier restorative loading of implants. Most commercially available implants depend on biomechanical interlocking for anchorage. All implants must exhibit biomechanical as well as morphological compatibility [7,141]. As we have seen previously, Ti implants coated with CaP or inorganic or organic bone-like apatite possess both anchorage mechanisms, because (1) coated surfaces are normally rough which can facilitate the biomechanical anchorage (morphological compatibility) and (2) coated materials *per se* accommodate biochemical bonding (biological compatibility).

Bone fusing to titanium was first reported in 1940 by Bothe et al. [208]. Brånemark began extensive experimental studies in 1952 on the microscopic circulation of bone marrow healing. These studies led to dental implant application in early 1960; 10-year implant integration was established in dogs without significant adverse reactions to hard or soft tissues. Studies in humans began in 1965, were followed for 10 years, and reported on in 1977 [209]. Osteointegration, as first defined by Brånemark, denotes at least some direct contact between vital bones with the surface of an implant at the light microscopic level of magnification [210]. The percentage of direct bone–implant contact is variable. To determine osseointegration, the implant must be removed and evaluated under a microscope. Rigid fixation defines the clinical aspect of this microscopic bone contact with an implant and is the absence of mobility with 1–500g force applied in a vertical or horizontal direction. Rigid fixation is the clinical result of a direct bone interface, but has also been reported with fibrous tissue interfaces [210]. Osteointegration was originally defined as a direct structural and functional connection between ordered living bone and the surface of a load-carrying artificial implant (which is typically made of titanium materials). It is now said that an implant is regarded as osteointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact. In practice, this means that in osteointegration there is an anchorage mechanism, whereby nonvital components can be reliably and predictably incorporated into living bone, and that this anchorage can persist under all normal conditions of loading. Bioactive (or biochemical) retention can be

achieved in cases where the implant is coated with bioactive materials, like HA. These bioactive materials stimulate bone formation, leading to a physicochemical bond. If it is recognized that the implant is ankylosed with the bone, it is sometimes called biointegration instead of osteointegration [211].

For profound understanding of the osteointegration mechanism, there are several works reported. Fourteen titanium dental implants (Tioblast™) were implanted singly in the proximal tibia of New Zealand White rabbits for 120 days. A bone defect was surgically produced and filled with Bio-Oss® (which is a natural, osteoconductive bone substitute that promotes bone growth in periodontal and maxillofacial osseous defects), around six of these implants. After the animals were sacrificed and their organs harvested, bone segments were fixed, and methacrylate embedded after the push-in test had been performed. The results showed that (i) the implants were apically and coronally surrounded by bone, whether Bio-Oss® was used or not, (ii) fractures were evident through the newly formed bone and between the preexisting and newly formed bone, and (iii) detachment between the implant and the bone occurred at the coronal extremity of the implants and along its cervical region. Based on these findings, it was concluded that the bone–titanium interface has a high resistance to loading, exhibiting a greater resistance than the newly formed bone [212].

The effect of a dual treatment of titanium implants and the subsequent bone response after implantation were investigated by Rønold et al. [213]. Coin-shaped CpTi implants were placed into the tibias of 12 rabbits. The implant was dually blasted with TiO₂ particles of two different sizes (i.e., finer particles of 22–28 µm in size and coarser particles of 180–220 µm in size). It was found that (i) the Ti surface blasted with coarse particles showed a significantly better functional attachment than the fine surface and (ii) the Ti surface blasted with fine particles showed lower retention in bone, indicating that there is a positive correlation between the topographical and mechanical evaluation of the surfaces [213].

In cementless fixation systems, surface character is an important factor. Alkali and heat treatments of titanium have been shown to produce strong bonding to bone and a higher ongrowth rate. With regard to the cementless hip stem, Nishiguchi et al. [214] examined the effect of alkali and heat treatments on titanium rods in an intramedullary rabbit femur model. Half of the implants were immersed in 5 mol/L sodium hydroxide solution and heated at 600°C for 1 h, and the other half were untreated. The bone–implant interfaces were evaluated at 3, 6, and 12 weeks after implantation. Pullout tests showed that the treated implants had a significantly higher bonding strength to bone than the untreated implants at each time point. As postoperative time elapsed, histological examination revealed that new bone formed on the surface of both types of implants, but significantly more bone made direct contact with the surface of the treated implants. At 12 weeks, approximately 56% of the whole surface of the treated implants was covered with the bone. Based on aforementioned results, it was concluded that (i) alkali-treated and heat-treated titanium create strong bone bonding and a high affinity to bone, as opposed to a conventional mechanical interlocking mechanism, and (ii) alkali and heat treatments of titanium may be suitable surface treatments for cementless joint replacement implants [214].

Several factors influence the healing process and the long-term mechanical stability of cementless fixed implants, such as bone remodeling and mineralization processes [215]. Histomorphometric and bone hardness measurements were taken in implants inserted in sheep femoral cortical bone at different times to compare the *in vivo* osseointegration of titanium screws with the following surface treatments: machined (Ti-MA); acid etched with 25 vol% of HNO₃ solution for 1 h (Ti-HF); HA vacuum plasma spray (Ti-HA); and CaP anodization (with 0.06 mL/L β -glycerophosphate plus 0.3 mL/L calcium acetate at 275 V and 50 mA/cm²), followed by a 300°C autoclave-hydrothermal treatment for 2 h (Ti-AM/HA). It was reported that (i) the BIC of Ti-HF was lower than that of the other surface treatments at both experimental times, (ii) significant differences in mineral apposition rate were also found between the different experimental times for Ti-MA and Ti-HF, demonstrating that bone growth had slowed inside the screw threads of Ti-HA and Ti-AM/HA after 12 weeks, (iii) no bone microhardness changes in preexisting host bone were found, while Ti-MA showed the lowest value for the inner thread area at 8 weeks. Based on these findings, it was confirmed that osteointegration may be accelerated by adequate surface roughness and a bioactive ceramic coating, such as CaP anodization followed by a hydrothermal treatment, which enhances bone interlocking and mineralization [215].

Fujibayashi et al. [216] demonstrated that bone formation took place after 12-month implantation in the muscles of beagle dogs and reported that chemically and thermally treated plasma-sprayed porous titanium surfaces exhibited an intrinsic osteoinductivity. Takemoto et al. [217] tested porous plasma-sprayed Ti blocks for the following characteristics: porosity of 41%, pore size of a ranging between 300 and 500 μ m, and yield compressive strength of 85.2 MPa. Three types of surface treatments were applied (1) alkali (in NaOH solution at 60°C for 24 h) and heat treatment (600°C for 1 h, followed by a furnace cooling), (2) alkali, hot water, and heat treatment, and (3) alkali, dilute 40°C HCl for 24 h, hot water, and heat treatment. The osteoinductivity of the materials implanted in the back muscles of adult beagle dogs was examined at 3, 6, and 12 months. It was found that (i) the alkali-acid/heat-treated porous bioactive titanium implant had the highest osteoinductivity, with induction of a large amount of bone formation within 3 months, (ii) the dilute HCl treatment was considered to give both chemical (titanium formation and sodium removal) and topographic (etching) effects on the titanium surface, and (iii) adding the dilute HCl treatment to the conventional chemical and thermal treatments is a promising candidate for advanced surface treatment of porous titanium implants [217,218].

A number of experimental and clinical data on so-called oxidized implants have reported promising outcomes, as we have previously reviewed. However, little has been investigated on the role of the surface oxide properties and osseointegration mechanism of the oxidized implant. Sul et al. [219] recently proposed two action mechanisms for osseointegration of oxidized implants, that is, (1) mechanical interlocking through bone growth in pores/other surface irregularities and (2) biochemical bonding. Two groups of oxidized implants were prepared using a microarc oxidation process and were then inserted into rabbit bone. One group consisted of

magnesium ion incorporated implants, and the other consisted of TiO_2 stoichiometry implants. It was reported that (i) after 6 weeks of follow up, the mean peak values for removal torque of the Mg-incorporated-Ti implants dominated significantly over the TiO_2/Ti implants, (ii) bonding failure generally occurred in the bone away from the bone-to-implant interface for the Mg-incorporated-Ti implant and mainly occurred at the bone-to-implant interface for the TiO_2/Ti implant which consisted mainly of TiO_2 chemistry and significantly rougher surfaces, as compared to the Mg-incorporated-Ti implant, and (iii) between bone and the Mg-incorporated-Ti implant surface, ionic movements, and ion concentrations gradient were detected. It was therefore concluded that the surface chemistry—mediated biochemical bonding can be theorized for explaining the oxidized bioactive implants [219]. Lim and Oshida et al. [185] investigated the surface characteristics of acid-treated and alkali-treated CpTi. It was reported that (i) acid-treated CpTi was covered with rutile-type TiO_2 with high hydrophobicity (in other words, less surface activity), whereas (ii) oxide film formed on the alkali-treated CpTi surface was identified to be an anatase type dominantly with a trace amount of rutile, which exhibited high hydrophilicity (i.e., high surface energy).

For the last 15 years, orthopedic implants have been coated with HA to improve implant fixation. The osteoconductive effect of HA coatings has been demonstrated in experimental and clinical studies. However, there are ongoing developments to improve the quality of HA coatings. Aebli et al. [220] investigated whether a rough and highly crystalline HA coating applied by vacuum plasma spraying had a positive effect on the osseointegration of special, high-grade titanium (Ti) implants with the same surface roughness. Ti alloy implants were vacuum plasma spray-coated with high-grade Ti or HA. The osseointegration of the implants was evaluated by light microscopy or pullout tests after 1, 2, and 4 weeks of unloaded implantation in the cancellous bone of 18 sheep. It was found that (i) the interface shear strength increased significantly over all time intervals, (ii) by 4 weeks, values had reached $\sim 10 \text{ N/mm}^2$, but (iii) the difference between the coatings was not significant at any time interval, and (iv) direct bone—implant contact was significantly different between the coatings after 2 and 4 weeks, and reached 46% for Ti and 68% for HA implants by 4 weeks. Therefore, it was indicated that the use of a rough and highly crystalline HA coating, applied by the vacuum plasma spray method, enhances early osseointegration [220].

Stewart et al. [221] investigated the effects of a plasma-sprayed HA/TCP coating on osseointegration of plasma-sprayed titanium alloy implants in a lapine, distal femoral intramedullary model. The effects of the HA/TCP coating were assessed at 1, 3, and 6 months after implant placement. The HA/TCP coating significantly increased new bone apposition onto the implant surfaces at all time points. The ceramic coating also stimulated intramedullary bone formation at the middle and distal levels of the implants. There was no associated increase in pullout strength at either 3 or 6 months; however, postpullout evaluation of the implants indicated that the HA/TCP coating itself was not the primary site of construct failure. Rather, failure was most commonly observed through the periprosthetic osseous struts that bridged the medullary cavity. It was therefore concluded that the osteoconductive

activity of HA/TCP coating on plasma-sprayed titanium alloy implant surfaces may have considerable clinical relevance to early host–implant interactions, by accelerating the establishment of a stable prosthesis–bone interface [221].

The *in vivo* behavior of a porous Ti–6Al–4V material that was produced by a positive replica technique, with and without an octacalcium phosphate coating, has been studied in both the back muscle and femur of goats by Habibovic et al. [222]. Macro- and microporous biphasic CaP ceramic, known to be both osteoconductive and able to induce ectopic bone formation, was used for comparison. The three groups of materials (Ti–6Al–4V, octacalcium phosphate coated-Ti–6Al–4V and biphasic CaP ceramic) were implanted transcortically and intramuscularly for 6 and 12 weeks in 10 adult Dutch milk goats in order to study their osteointegration and osteoinductive potential. It was found that (i), in femoral defects, both octacalcium phosphate coated-Ti–6Al–4V and biphasic CaP ceramic performed better than the uncoated Ti–6Al–4V at both time points, (ii) biphasic CaP ceramic showed a higher bone amount than octacalcium phosphate coated-Ti–6Al–4V after 6 weeks of implantation, while after 12 weeks, this difference was no longer significant, (iii) ectopic bone formation was found in both octacalcium phosphate coated-Ti–6Al–4V and biphasic CaP ceramic implants after 6 and 12 weeks, and (iv) ectopic bone formation was not found in uncoated titanium alloy implants, suggesting that the presence of CaP is important for bone induction. [222].

The osteointegration of copper vapor laser-superfinished titanium alloy (Ti–6Al–4V) implants with pore sizes of 25, 50, and 200 μm was evaluated in a rabbit intramedullary model by Stangl et al. [223]. Control implants were prepared by corundum blasting. Each animal received all four different implants in both femora and humeri. Using static and dynamic histomorphometry, the bone–implant interface and the peri-implant bone tissue were examined 3, 6, and 12 weeks post-implantation. Among the laser-superfinished implants, it was reported that total bone–implant contact was smallest for the 25- μm pores, and was similar for 50- and 200- μm pore sizes at all time points; however, all laser-superfinished surfaces were inferior to corundum-blasted control implants in terms of bone–implant contact. Implants with 25- μm pores showed the highest amount of peri-implant bone volume at all time points, indicating that the amount of peri-implant bone was not correlated with the quality of the bone–implant interface. Accordingly, it was concluded that although laser-superfinished implants were not superior to the corundum-blasted control implants in terms of osteointegration, understanding of the mechanisms of bone remodeling within pores of various sizes was advanced, and optimal implant surfaces can be further developed with the help of modern laser technology [223].

There is another work using the laser technology for surface modification. Götz et al. [224] examined the osteointegration of laser-textured Ti–6Al–4V implants with pore sizes of 100, 200, and 300 μm , specifically comparing 200- μm implants with polished and corundum-blasted surfaces in a rabbit transcortical model. Using a distal and proximal implantation site in the distal femoral cortex, each animal received all four different implants in both femora. The bone-implant interface and the newly formed bone tissue within the pores and in peri-implant bone tissue were

examined 3, 6, and 12 weeks postimplantation by static and dynamic histomorphometry. It was shown that (i) additional surface blasting of laser-textured Ti–6Al–4V implants with 200- μ m pores resulted in a profound improvement in osteointegration at 12-week postimplantation, (ii) although lamellar bone formation was found in pores of all sizes, the amount of lamellar bone within the pores was linearly related to the pore size, (iii) in 100- μ m pores, bone remodeling occurred with a pronounced time lag relative to larger pores, and (iv) implants with 300- μ m pores showed a delayed osteointegration compared with 200- μ m pores. Therefore, it was concluded that 200 μ m may be the optimal pore size for laser-textured Ti–6Al–4 V implants, and that laser treating in combination with surface blasting may be a very interesting technology for the structuring of implant surfaces [224].

There are some researches done on method or technique to evaluate/examine the osteointegration [225–228]. Since bone should be observed to grow into the porous structure of the coating, yielding direct evidence of a mechanism of the bone–implant interface, it was proposed to employ the advanced various analytical devices including dual-beam focused ion beam microscopy, SEM, transmission electron microscopy (TEM), and X-ray energy dispersive spectrometer [225]. Stenport et al. [226] conducted comparison tests of tissue integration to CpTi and Ti–6Al–4V implants using various three-dimensional biomechanical and two-dimensional histomorphometrical techniques, and mentioned the loosening torque during *in vivo* removal torque in rabbits. It was found that significantly higher mean values for the removal torque and shear strength tests were observed for the CpTi implants compared to Ti–6Al–4V implants. In order to chronologically examine the titanium–bone interfaces and to clarify the process of osteointegration, Morinaga et al. [227] utilized light microscopy, TEM, quantitative tomography (QCT), and microcomputed tomography (micro-QCT). Experimental implants (Ti-coating plastic implants) were placed into tibiae of 8-week-old rats. It was reported that (i) bone formation in osteointegration of Ti implants did not occur from the surfaces of the implant or preexisting bone, but it was likely that bone formation progressed at a site a small distance away from the surface, (ii) small bone fragments adhered to each other and transformed into reticular-shaped bone, and finally these bones became lamellar bone [224]. Kerner et al. [228] assessed *in vivo* new bone formation around Ti–6Al–4V alloy implants chemically grafted with macromolecules bearing ionic sulfonate and/or carboxylate groups. Unmodified and grafted Ti–6Al–4V implants were placed bilaterally into rabbit femoral condyle. It was found that (i) the BIC was the lowest (13.4%) for the implants modified with grafted carboxylate only, (ii) the value of BIC on the implants with 20% sulfonate was significantly lower than that observed on 100% sulfonate surfaces, (iii) after both 4 and 12 weeks postimplantation, the BIC value for implants with more than 50% sulfonate was similar to that obtained with the unmodified Ti–6Al–4V, and (iv) the grafted Ti–6Al–4V alloy exhibiting either 100% sulfonate or carboxylate and sulfonate (50% each) groups promoted bone formation. Such materials are of clinical interest because they do not promote bacteria adhesion but they support new bone formation, a condition which can lead to osteointegration of bone implants while preventing peri-implant infections [228].

7.10 Some Adverse Factors for Loosening Implants

Early implant instability has been proposed as a critical factor in the onset and progression of aseptic loosening and periprosthetic osteolysis in total joint arthroplasties. As was seen in Chapter 6, macrophages stimulated with cyclic mechanical strain release inflammatory mediators. But little is known about the response of these cells to mechanical strain with particles, which is often a component of the physical environment of the cell. Fujishiro et al. [229] studied the production of PGE₂, an important mediator in aseptic loosening and periprosthetic osteolysis in total joint arthroplasties, for human macrophages treated with mechanical stretch alone, titanium particles alone, and mechanical stretch and particles combined. A combination of mechanical stretch and titanium particles resulted in a statistically synergistic elevation of levels of PGE₂ compared with the levels found with either stretch or particles alone. It was hence suggested that, while mechanical strain may be one of the primary factors responsible for macrophage activation and periprosthetic osteolysis, mechanical strain with particle load may contribute significantly to the osteolytic potential of macrophages *in vitro* [229].

Corrosion of implant alloys releasing metal ions has the potential to cause adverse tissue reactions and implant failure. Lin et al. [230] hypothesized that macrophage cells and their released reactive chemical species affect the corrosion property of Ti–6Al–4V. It was reported that (i) there was no difference in the charge transfer in the presence and absence of cells, (ii) the alloy had the lowest charge transfer and metal ion release with activated cells as follows; Ti < 10 ppb, V < 2 ppb, attributing to an enhancement of the surface oxides by the reactive chemical species. It was concluded that macrophage cells and reactive chemical species reduced the corrosion of Ti–6Al–4V alloys [230].

Prosthetic and osteosynthetic implants from metal alloys will be indispensable in orthopedic surgery, as long as tissue engineering and biodegradable bone substitutes do not lead to products that will be applied in clinical routines for the repair of bone, cartilage, and joint defects. Therefore, the elucidation of the interactions between the periprosthetic tissues and the implant remains of clinical relevance, and several factors are known to affect the longevity of implants. Sommer et al. [231] studied the effects of metal particles and surface topography on the recruitment of osteoclasts *in vitro* in a coculture of osteoblasts and bone marrow cells. It was reported that (i) the cells were grown in the presence of particles of different sizes and chemical compositions, or on metal disks with polished or sandblasted surfaces, respectively, (ii) at the end of the culture, newly formed osteoclasts were counted, (iii) osteoclastogenesis was reduced when particles were added directly to the coculture, and (iv) in cocultures grown on sandblasted surfaces, osteoclasts developed at higher rates than they did in cultures on polished surfaces. It was therefore summarized that the wear particles and implant surfaces affect osteoclastogenesis, and thus may be involved in the induction of local bone resorption and the formation of osteolytic lesions, leading eventually to the loosening of orthopedic implants [231].

The load of the implant should preferably be in the longitudinal direction. Thus it is important to avoid rotational or cantilever forces once the implant has integrated. If forces are distributed in the longitudinal direction, even very high loads can be withstood by the implant during many years of function [232]. Loss of integration can be obtained by overload, torsional forces, or direct trauma to the implant. Overload might be the result of the long extensions of the bar construction or by misplaced implants. Minor torsion forces might induce microfractures in the bone that with time can rupture the delicate integration. Lack of adequate counterforces during tightening of the abutment might result in immediate implant loss. Tightening of individual magnets used as retentions without counterhold might as well cause implant failures [232]. The quantity and also the quality of bone might determine the force necessary to loosen an implant. The most well-known cause for implant failure is the bone that has been irradiated as part of cancer treatment. Chemotherapy also affects implant survival to a similar degree as radiotherapy. Other factors that might affect implant survival are osteoporosis, steroid medication, and diabetes mellitus [233].

7.11 Nonmetallic Implants

For most esthetic reasons, recently nonmetallic implants are receiving attention. Further, ceramic materials are currently being used for implant fabrication: single crystals of alumina [234,235], polycrystals of zirconia [236–238], titania [239], or combination of these three oxides [240]. One remarkable advantage of these ceramic implants is their esthetic appearance of a bright white color. Again referring to Figure 6.1 in Chapter 6 of this book, we can identify these ceramics (partially stabilized zirconia and A) at further away from T group, suggesting that the potential interfacial stress, $\Delta\sigma$, could be much higher than previous $\Delta\sigma$ generated between T and B. It is crucial that this higher risk for interfacial debonding or even fracture on ceramic implants or alveolar bone should be carefully taken into consideration when ceramic implants are placed.

References

- [1] Misch CE, editor. Implant dentistry. 2nd ed. St. Louis, MO: Mosby, an Affiliate of Elsevier; 1999.
- [2] Burden DJ, Eedy DJ. Orthodontic headgear related to allergic contact dermatitis; a case report. *Br Dent J* 1991;170:447–8.
- [3] Veien NK, Borchorst E, Hattcel T, Laurberg G. Stomatitis or systemically induced contact dermatitis from metal wire in orthodontic materials. *Contact Dermatitis* 1994;30:210–3.
- [4] BS ISO 7206-10:2003. Partial and total hip-joint prostheses. Determination of resistance to static load of modular femoral heads. December 17, 2003
- [5] Kasemo B, Lausmaa J. Biomaterials and implant surfaces: a surface science approach. *Int J Oral Maxillofac Implants* 1988;3:247–59.

- [6] Albrektsson T, Brånemark PI, Hansson HA, Lindstrom J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. *Acta Orthop Scand* 1981;52:155–70.
- [7] Albrektsson T. Direct bone anchorage of dental implants. *J Prosth Dent* 1983;50:255–61.
- [8] Davies JE. Understanding peri-implant endosseous healing. *J Dent Edu* 2003;67:932–49.
- [9] Eriksson C, Broberg M, Nygren H, Öster L. Novel *in vivo* method for evaluation of healing around implants in bone. *J Biomed Mater Res* 2003;66A:662–8.
- [10] Osborn JF, Kovacs E, Kallenberger A. Hydroxylapatit Keramik—Entwicklung lines neuen Biowerkstoffes und erste tierexperimentelle Ergebnisse. *Dtsch Zahnärztl Z* 1980;5:54–6.
- [11] Steinemann S. Werkstoff titan. In: Schroeder A, Sutter F, Krekeler G, editors. *Orale implantologie*. Stuttgart: Thieme; 1988.
- [12] Sugarawa A. Self-healing calcium phosphates—the properties and the applications for bone regeneration. *Jpn J Maxillo Facial Implants* 2005;4:41–9.
- [13] Scarano A, Piattelli M, Vrespa G, Petrone G, Iezzi G, Piattelli A. Bone healing around titanium and titanium nitride-coated dental implants with three surfaces: an experimental study in rats. *Clin Implant Dent Relat Res* 2003;5:103–11.
- [14] Lee JE, Heo SJ, Koak JY, Kim SK, Han CH, Lee SJ. Healing response of cortical and cancellous bone around titanium implants. *Int J Oral Maxillofac Implants* 2009;24:655–62.
- [15] Franco RL, Chiesa R, de Oliveira PT, Beloti MM, Rosa AL. Bone response to a Ca- and P-enriched titanium surface obtained by anodization. *Braz Dent J* 2008;19:15–20.
- [16] Colnot C, Romero DM, Huang S, Rahman J, Currey JA, Nanci A, et al. Molecular analysis off healing at a bone–implant interface. *J Dent Res* 2007;86:862–7.
- [17] Lin DJ, Chuang CC, Cher Lin JH, Lee JW, Ju CP, Yin HS. Bone formation at the surface of low modulus Ti–7.5Mo implants in rabbit femur. *Biomaterials* 2007;28:2582–9.
- [18] Sato N, Kubo K, Yamada M, Hori N, Suzuki T, Maeda H, et al. Osteoblast mechanoreponses on Ti with different surface topographies. *J Dent Res* 2009;88:812–6.
- [19] Takemoto S, Yamamoto T, Tsuru K, Hayakawa S, Osaka A, Takashima S. Platelet adhesion on titanium oxide gels: effect of surface oxidation. *Biomaterials* 2004;25:3485–92.
- [20] Huang N, Yang P, Leng YX, Chen JY, Sun H, Wang J, et al. Hemocompatibility of titanium oxide films. *Biomaterials* 2003;24:2177–87.
- [21] Dion I, Baquey C, Monties JR, Havlik P. Harmocompatibility of Ti6Al4V alloy. *Biomaterials* 1993;14:122–6.
- [22] Eriksson AS, Bjursten LM, Ericson LE, Thomsen P. Hollow implants in soft tissue allowing quantitative studies of cells and fluid at the implant interface. *Biomaterials* 1988;9:86–90.
- [23] Eriksson AS, Thomsen P. Leukotriene B4, interleukin 1 and leucocyte accumulation in titanium and PTFE chambers after implantation in the rat abdominal wall. *Biomaterials* 1991;12:827–30.
- [24] Elwing H, Tengvall P, Askendal A, Lunstroem I. Lens on surface: a versatile method for the investigation of plasma protein exchange reactions on solid surfaces. *J Biomater Sci Polym Educ* 1991;3:7–16.
- [25] Graham TR, Dasse K, Coumbe A, Salih V, Marrinan MT, Frazier OH, et al. Neointimal development on textured biomaterial surfaces during clinical use of an implantable left ventricular assist device. *Eur J Cardiothorac Surg* 1990;4:182–90.
- [26] Ellingen JE. A study on the mechanism of protein adsorption to TiO₂. *Biomaterials* 1991;12:593–6.
- [27] Sunny MC, Sharma CP. Titanium–protein interaction changes with oxide layer thickness. *J Biomater Appl* 1991;6:89–98.

- [28] Merritt K, Edwards CR, Brown SA. Use of an enzyme linked immunosorbent assay (ELISA) for quantification of proteins on the surface of materials. *J Biomed Mater Res* 1988;22:99–109.
- [29] Muramatsu K, Uchida M, Kim H-M, Fujisawa A, Kokubo T. Thromboresistance of alkali- and heat-treated titanium metal formed with apatite. *J Biomed Mater Res* 2003;65A:409–16.
- [30] Suska F, Gretzer C, Esposito M, Tengvall P, Thomsen P. Monocyte viability on titanium and copper coated titanium. *Biomaterials* 2005;26:5942–50.
- [31] Maitz MF, Shevchenko N. Plasma-immersion ion-implanted nitinol surface with depressed nickel concentration for implants in blood. *J Biomed Mater Res* 2006;76A:356–65.
- [32] Martinesi M, Bruni S, Stio M, Treves C, Borgioli F. *In vitro* interaction between surface-treated Ti–6Al–4V titanium alloy and human peripheral blood mononuclear cells. *J Biomed Mater Res* 2005;74A:197–207.
- [33] Thor A, Rasmusson L, Wennerberg A, Thomsen P, Hirsch JM, Nilsson B, et al. The role of whole blood in thrombin in contact with various titanium surfaces. *Biomaterials* 2007;28:966–74.
- [34] Eriksson C, Lausmaa J, Nygren H. Interactions between human whole blood and modified TiO₂-surfaces: influence of surface topography and oxide thickness on leukocyte adhesion and activation. *Biomaterials* 2001;22:1987–96.
- [35] Kasemo B, Lausmaa J. Surfaces science aspects on inorganic biomaterials. *CRC Crit Rev Biocomp* 1986;2:335–80.
- [36] Masuda T, Salvi GE, Offenbacher S, Fleton D, Cooper LF. Cell and matrix reactions at titanium implants in surgically prepared rat tibiae. *Int J Oral Maxillofac Implants* 1997;1:472–85.
- [37] Rosengren A, Johansson BR, Danielsen N, Thomsen P, Ericson LE. Immunohistochemical studies on the distribution of albumin, fibrinogen, fibronectin, IgG and collagen around PTFE and titanium implants. *Biomaterials* 1996;17:1779–86.
- [38] Chehroudi B, McDonnell D, Brunette DM. The effects of micromachined surfaces on formation of bonelike tissue on subcutaneous implants as assessed by radiography and computer image processing. *J Biomed Mater Res* 1997;34:279–90.
- [39] Larsson C, Thomsen P, Lausmaa J, Rodahl M, Kasemo B, Ericson LE. Bone response to surface modified implants: studies on electropolished implants with different oxide thickness and morphology. *Biomaterials* 1994;15:1062–74.
- [40] Wälivaara B, Askendal A, Lundström I, Tengvall P. Blood protein interaction with titanium surfaces. *J Biomater Sci Polym Edn* 1996;8:41–8.
- [41] Kanagaraja S, Lundström I, Nygren H, Tengvall P. Platelet binding and protein adsorption to titanium and gold after short time exposure to heparinized plasma and whole blood. *Biomaterials* 1996;17:2225–32.
- [42] Nygren H, Eriksson C, Lausmaa J. Adhesion and activation of platelets and polymorphonuclear granulocyte cells at TiO₂ surfaces. *J Lab Clin Med* 1997;129:35–46.
- [43] Tan P, Lusinskas FW, Homer-Vanniasinkam S. Cellular and molecular mechanisms of inflammation and thrombosis. *Eur J Vasc Endovasc Surg* 1999;17:373–89.
- [44] Brown KK, Henson PM, Maclof J, Moyle M, Ely JA, Worthen GS. Neutrophil–platelet adhesion: relative roles of platelet P-selection and neutrophil $\beta 2$ (CD18) integrins. *Am J Resp Cell Mol Biol* 1998;18:100–10.
- [45] De La Cruz C, Haimovich B, Greco RS. Immobilized IgG and fibrinogen differentially affect the cytoskeletal organization and bactericidal function of adherent neutrophils. *J Surg Res* 1998;80:28–34.

- [46] Berton G, Yan SR, Fumagalli L, Lowell CA. Neutrophil activation by adhesion: mechanisms and pathophysiological implications. *Int J Clin Lab Res* 1996;26:160–77.
- [47] Fröhlich D, Spertini O, Moser R. The $\text{Fc}\gamma$ receptor-mediated respiratory burst of rolling neutrophils to cytokine-activated, immune complex-bearing endothelial cells depends on L-selection but not E-selection. *Blood* 1998;91:2558–68.
- [48] Hansson H-A, Albrektsson T, Brånemark P-I. Structural aspects of the interface between tissue and titanium implants. *J Prosthet Dent* 1983;50:108–13.
- [49] Albrektsson T, Brånemark P-I, Hansson H-A, Kasemo B, Larsson K, Lundström I, et al. The interface zone of inorganic implants *in vivo*: titanium implants in bone. *Ann Biomed Eng* 1983;11:1–27.
- [50] Linder L, Albrektsson T, Brånemark P-I, Hansson H-A, Ivarsson B, Jönsson U, et al. Electron microscopic analysis of the bone–titanium interface. *Acta Orthop Scand* 1983;54:45–52.
- [51] Kempien B, Schulte W, Kleineikenscheidt H, Linder K, Scareyka R, Heimke G. Lichtoptische und rasterelektronen-mikroskopische Untersuchungen an der grenzfläche von Implantaten aus Aluminium-oxidkeramik im Unterkieferknochen von Hunden. *Dtsch Zahnärztl Z* 1978;33:332–40.
- [52] Albrektsson T, Hansson H-A, Ivarsson B. Interface analysis of titanium and zirconium bone implants. *Biomaterials* 1985;6:97–101.
- [53] Albrektsson T, Hansson H-A. An ultrastructural characterization of the interface between bone and sputtered titanium or stainless steel surfaces. *Biomaterials* 1986;7:201–5.
- [54] Parsegian VA. Molecular forces governing tight contact between cellular surfaces and substrates. *J Prosthet Dent* 1983;49:838–42.
- [55] Kasemo B. Biocompatibility of titanium implants: surface science aspects. *J Prosthet Dent* 1983;49:832–7.
- [56] McQueen D, Sundgren J-E, Ivarsson B, Lundström I, af Ekenstam B, Svensson A, et al. Auger electroscopic studies of titanium implants. In: Lee AJC, Albrektsson T, Brånemark P-I, editors. *Clinical applications of biomaterials*. Chichester, UK: John Wiley & Sons; 1982. p. 179–85.
- [57] Abe M. Oxides and hydrous oxides of multivalent metals as inorganic ion exchangers. In: Clearfield A, editor. *Inorganic Ion Exchange Materials*. Boca Raton, FL: CRC Press; 1982. p. 161–273.
- [58] Bernardi G, Kawasaki T. Chromatography of polypeptides and proteins on hydroxylapatite columns. *Biochim Biophys Acta* 1968;160:301–10.
- [59] Embery G, Rølla G. Interaction between sulphated macromolecules and hydroxyapatite studied by infrared spectroscopy. *Acta Odontol Scand* 1980;38:105–8.
- [60] Rosengren A, Johansson BR, Thomsen P, Ericson LE. A method for immunolocalization of extracellular proteins in association with the implant–soft tissue interface. *Biomaterials* 1994;15:17–24.
- [61] Röstlund T, Thomsen P, Bjursten LM, Ericson LE. Difference in tissue response to nitrogen-ion implanted titanium and c.p. titanium in the abdominal wall of the rat. *J Biomed Mater Res* 1990;24:847–60.
- [62] Eriksson AS, Lindblad R, Ericson LE, Thomsen P. Distribution of cells around implants in soft tissue in the rat. *J Mater Sci Mater Med* 1994;5:269–78.
- [63] Johansson CB, Albrektsson T, Ericson LE, Thomsen P. A quantitative comparison of the cell response to commercially pure titanium and Ti6Al4V implants in the abdominal wall of the rat. *J Mater Sci Mater Med* 1992;3:126–36.

- [64] Anderson JM, Miller KM. Biomaterial biocompatibility and the macrophase. *Biomaterials* 1984;5:5–10.
- [65] Miller KM, Anderson JM. *In vitro* stimulation of fibroblast activity by factors generated from human monocytes activated by biomedical polymers. *J Biomed Mater Res* 1989;23:911–30.
- [66] Bonfield TL, Colton E, Anderson JM. Plasma protein adsorbed biomedical polymers: activation of human monocytes and induction of interleukin. *J Biomed Mater Res* 1989;23:535–48.
- [67] Healy KE, Ducheyne P. Hydration and preferential molecular adsorption on titanium *in vitro*. *Biomaterials* 1992;13:553–61.
- [68] Zeng H, Chittur KK, Lacefield WR. Analysis of bovine serum albumin adsorption on calcium phosphate and titanium surfaces. *Biomaterials* 1999;20:377–84.
- [69] MacDonald DE, Deo N, Mrkovic B, Stranick M, Somasundaran P. Adsorption and dissolution behavior of human plasma fibronectin on thermally and chemically modified titanium dioxide particles. *Biomaterials* 2002;23:1269–79.
- [70] Deligianni DD, Katsala N, Ladas S, Sotiropoulou D, Amedee J, Missirlis YF. Effect of surface roughness of the titanium alloy Ti–6Al–4V on human bone marrow cell response and on protein adsorption. *Biomaterials* 2001;22:1241–51.
- [71] Yang Y, Cavin R, Ong LJ. Protein adsorption on titanium surfaces and their effect on osteoblast attachment. *J Biomed Mater Res* 2003;67A:344–9.
- [72] Schenk RK, Buser D. Osseointegration: a reality. *Periodontology* 1998;17:22–35.
- [73] Larsson C, Esposito M, Liao H, Thomsen P. The titanium–bone interface *in vivo*. In: Brunette DM, Tengvall P, Textor M, Thomsen, editors. *Titanium in medicine: materials science, surface science, engineering, biological responses, and medical applications*. New York, NY: Springer; 2001. p. 587–648.
- [74] Masuda T, Yliheikkilä PK, Fleton DA, Cooper LF. Generalizations regarding the process and phenomenon of osseointegration. Part I. *In vivo* studies. *Int J Oral Maxillofac Implant* 1998;13:17–29.
- [75] Oshida Y, Sachdeva R, Miyazaki S. Microanalytical characterization and surface modification of NiTi orthodontic archwires. *J Biomed Mater Eng* 1992;2:51–69.
- [76] Zinger O, Anselme K, Denzer A, Habersetzer P, Wieland M, Jeanfils J, et al. Time-dependent morphology and adhesion of osteoblastic cells on titanium model surfaces featuring scale-resolved topography. *Biomaterials* 2004;25:2695–711.
- [77] Leven RM, Virdi AS, Sumner DR. Patterns of gene expression in rat bone marrow stromal cells cultured on titanium alloy discs of different roughness. *J Biomed Mater Res* 2004;70A:391–401.
- [78] Li JP, Li SH, Van Blitterswijk CA, de Groot K. A novel porous Ti6Al4V: Characterization and cell attachment. *J Biomed Mater Res* 2005;73A:223–33.
- [79] Hughes Wassell DT, Embery G. Adsorption of bovine serum albumin on to titanium powder. *Biomaterials* 1996;17:859–64.
- [80] Webster TJ, Ergun C, Doremus RH, Lanford WA. Increased osteoblast adhesion on titanium-coated hydroxyapatite that forms CaTiO_3 . *J Biomed Mater Res* 2003;67A:975–80.
- [81] MacDonald DE, Rapuano BE, Deo N, Stranick M, Somasundaran P, Boskey AL. Thermal and chemical modification of titanium–aluminum–vanadium implant materials: effects on surface properties, glycoprotein adsorption, and MG63 cell attachment. *Biomaterials* 2004;25:3135–46.
- [82] Oshida Y, Sachdeva R, Miyazaki S. Changes in contact angles as a function of time on some pre-oxidized biomaterials. *J Mater Sci Mater Med* 1992;3:306–12.

- [83] Webster TJ, Ejirofor JU. Increased osteoblast adhesion on nanophase metals: Ti, Ti6Al4V, and CoCrMo. *Biomaterials* 2004;25:4731–9.
- [84] Jain R, von Recum AF. Fibroblast attachment to smooth and microtextured PET and thin CpTi films. *J Biomed Mater Res* 2004;68A:296–304.
- [85] Zhang YM, Bataillon-Linez P, Huang P, Zhao YM, Han Y, Traisnel M, et al. Surface analyses of micro-arc oxidized and hydrothermally treated titanium and effect on osteoblast behavior. *J Biomed Mater Res* 2004;68A:383–91.
- [86] Nayab SN, Jones FH, Olsen I. Human alveolar bone cell adhesion and growth on ion-implanted titanium. *J Biomed Mater Res* 2004;69A:651–7.
- [87] Maitz MF, Poon RWY, Liu XY, Pham M-T, Chu PK. Bioactivity of titanium following sodium plasma immersion ion implantation and deposition. *Biomaterials* 2005;26:5465–73.
- [88] Muhonen V, Heikkinen R, Danilov A, Jämsä T, Ilvesaro J, Tuukkanen J. The phase state of NiTi implant material affects osteoclastic attachment. *J Biomed Mater Res* 2005;75A:681–8.
- [89] Walboomers XF, Elder SE, Bumgardner JD, Jansen JA. Hydrodynamic compression of young and adult rat osteoblast-like cells on titanium fiber mesh. *J Biomed Mater Res* 2006;76A:16–24.
- [90] Clem WC, Konovalov VK, Chowdhury S, Vohra YK, Catledge SA, Bellis SL. Mesenchymal stem cell adhesion and spreading on microwave plasma-nitrided titanium alloy. *J Biomed Mater Res* 2006;76A:279–87.
- [91] Advincula MC, Rahemtulla FG, Advincula RC, Ada ET, Lemons JE, Bellis SL. Osteoblast adhesion and matrix mineralization on sol–gel-derived titanium oxide. *Biomaterials* 2006;27:2201–12.
- [92] Wälivaara B, Aronsson B-O, Rodahl M, Lausmaa J, Tengvall P. Titanium with different oxides: *in vitro* studies of protein adsorption and contact activation. *Biomaterials* 1994;15:827–34.
- [93] Brunette DM. The effects of implant surface topography on the behavior of cells. *Int J Oral Maxillofac Implants* 1988;3:231–46.
- [94] Meenaghan MA, Bielat KL, Budd TW, Scaaf NG, Nagahara K. Nature of metallic implant surfaces and the importance of their preparation. *Oral Maxillofac Surg Clin* 1991;3:765–73.
- [95] Meyle J, Wolburg H, von Recum AF. Surface micromorphology and cellular interactions. *J Biomater Appl* 1993;7:362–74.
- [96] Bowers KT, Keller JC, Randolph BA, Wick DG, Michaels CM. Optimization of surface micromorphology for enhanced osteoblast responses *in vitro*. *Int J Oral Maxillofac Implants* 1992;7:302–10.
- [97] Schwartz Z, Martin JY, Dean DD, Simpson J, Cochran DL, Boyan BD. Effect of titanium surface roughness on chondrocyte proliferation, matrix production, and differentiation depends on the state of cell maturation. *J Biomed Mater Res* 1996;30:145–55.
- [98] Ahmad M, Gawronski D, Blum J, Goldberg J, Gronowicz G. Differential response of human osteoblast-like cells to commercially pure (cp) titanium grades 1 and 4. *J Biomed Mater Res* 1999;46:121–31.
- [99] Khakbaznejad A, Chehroudi B, Brunette DM. Effects of titanium-coated micromachined grooved substrata on orienting layers of osteoblast-like cells and collagen fibers in culture. *J Biomed Mater Res* 2004;70A:206–18.
- [100] Zhu X, Chen J, Scheideler L, Reichl R, Geis-Gerstorf J. Effects of topography and composition of titanium surface oxides on osteoblast responses. *Biomaterials* 2004;25:4087–103.

- [101] Saldaña L, Vilaboa N, Vallés G, González-Cabrero J, Munuera L. Osteoblast response to thermally oxidized Ti6Al4V alloy. *J Biomed Mater Res* 2005;73A:97–107.
- [102] Kim HJ, Kim SH, Kim MS, Lee EJ, Oh HG, Oh WM, et al. Varying Ti–6Al–4V surface roughness induces different early morphologic and molecular responses in MG63 osteoblast-like cells. *J Biomed Mater Res* 2005;74A:366–73.
- [103] Meredith DS, Eschbach L, Wood MA, Riehle MO, Curtis ASG, Richards RG. Human fibroblast reactions to standard and electropolished titanium and Ti–6Al–7Nb and electropolished stainless steel. *J Biomed Mater Res* 2005;75A:541–55.
- [104] Nayab SN, Jones FH, Olsen I. Effects of calcium ion implantation on human bone cell interaction with titanium. *Biomaterials* 2005;26:4717–27.
- [105] Feng B, Chen J, Zhang X. Interaction of calcium and phosphate in apatite coating on titanium with serum albumin. *Biomaterials* 2002;23:2499–597.
- [106] Tetè S, Mastrangelo F, Bianchi A, Zizzari V, Scarano A. Collagen fiber orientation around machined titanium and zirconia dental implant necks: an animal study. *Int J Oral Maxillofac Implants* 2009;24:52–8.
- [107] Salohoglu U, Boynuegri D, Engin D, Duman AN, Gökalp P, Balos K. Bacterial adhesion and colonization differences between zirconium oxide and titanium alloys: an in vivo human study. *Int J Oral Maxillofac Implants* 2011;26:101–7.
- [108] Faghihi S, Azari F, Szpunar JA, Vali H, Tabrizian M. Titanium crystal orientation as a tool for the improved and regulated cell attachment. *J Biomed Mater Res A* 2009;91:656–62.
- [109] Kimura Y, Matsuoka K, Yoshinari M, Inoue T. Initial attachment of human oral keratinocytes cultured on zirconia or titanium. *Dent Mater J* 2012;31:346–53.
- [110] Pugdee K, Shibata Y, Yamamichi N, Tsutsumi H, Yoshinari M, Abiko Y, et al. Gene expression of MC3T3-E1 cells on fibronectin-immobilized titanium using tresyl chloride activation technique. *Dent Mater J* 2007;26:647–55.
- [111] Ko HC, Han JS, Bächle M, Jang JH, Shin SW, Kim DJ. Initial osteoblast-like cell response to pure titanium and zirconia/alumina ceramics. *Dent Mater* 2007;23:1349–55.
- [112] Rosa AL, Crippa GE, de Oliveria PT, Taba M, Lefebvre LP, Beloti MM. Human alveolar bone cell proliferation, expression of osteoblastic phenotype, and matrix mineralization on porous titanium produced by powder metallurgy. *Clin Oral Implants Res* 2009;20:472–81.
- [113] Shapira L, Klinger A, Tadir A, Wilensky A, Halabi A. Effect of niobium-containing titanium alloy on osteoblast behavior in culture. *Clin Oral Implants Res* 2009;20:578–82.
- [114] Wen X, Wang X, Zhang N. Microsurface of metallic biomaterials: a literature review. *J Biomed Mater Eng* 1996;6:173–89.
- [115] Keller JC, Dougherty WJ, Grotendorst GR, Wrightman JP. *In vitro* cell attachment to characterized CpTi surfaces. *Adhesion* 1989;28:115–33.
- [116] Keller JC, Wrightman JP, Dougherty WJ. Characterization of acid passivated CpTi surfaces. *J Dent Res* 1989;68:872.
- [117] Keller JC, Draughn RA, Wrightman JP, Dougherty WJ. Characterization of sterilized CP titanium implant surfaces. *Int J Oral Maxillofac Implants* 1990;5:360–9.
- [118] Schroeder A, Van der Zypen E, Stich H, Sutter F. The reactions of bone, connective tissue and epithelium to endosteal implants with titanium sprayed surfaces. *J Maxillofac Surg* 1981;9:15–25.
- [119] Buser D, Schenk RK, Steinemann S, Fiorellinni JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. *J Biomed Mater Res* 1991;25:889–902.

- [120] Rich A, Harris AK. Anomalous preferences of cultured macrophages for hydrophobic and roughened substrata. *J Cell Sci* 1981;50:1–7.
- [121] Murray DW, Rae T, Rushton N. The influence of the surface energy and roughness of implants on bone resorption. *J Bone Joint Surg* 1989;71B:632–7.
- [122] Jansen JA, van der Waerden JPCM, Wolke JGC. Histologic investigation of the biologic behavior of different hydroxyapatite plasma-coatings in rabbits. *J Biomed Mater Res* 1993;27:603–10.
- [123] Wang BC, Lee TM, Chang E, Yang CY. The shear strength and the failure mode of plasma-sprayed hydroxyapatite coating to bone: the effect of coating thickness. *J Biomed Mater Res* 1993;27:1315–27.
- [124] Steinemann SG, Eulenberger J, Maeusli PA, Schoeder A. Biological and biomechanical performances of biomaterials. Amsterdam: Elsevier Science; 1986. p. 409–14.
- [125] Hayashi K, Inadome T, Mashima T, Sugioka Y. Comparison of bone–implant interface shear strength of solid hydroxyapatite and hydroxyapatite-coated titanium implants. *J Biomed Mater Res* 1993;27:557–63.
- [126] Thomas KA, Cook SD. An evaluation of variable influencing implant fixation by direct bone apposition. *J Biomed Mater Res* 1985;19:875–901.
- [127] Li J. Behavior of titanium and titanium-based ceramics *in vitro* and *in vivo*. *Biomaterials* 1993;14:229–32.
- [128] Oshida Y. Requirements for successful, biofunctional implants. In: Yahia L'H, editor. International symposium on advanced biomaterials. Montréal, Canada; 2000. p. 5.
- [129] Cherhoudi B, Gould TR, Brunette DM. Effects of a grooved epoxy substratum on epithelial behavior *in vivo* and *in vitro*. *J Biomed Mater Res* 1988;22:459–77.
- [130] von Recum AF. New aspects of biocompatibility: motion at the interface. In: Heimke G, Soltesz U, Lee AJC, editors. Clinical implant materials. Amsterdam: Elsevier Science; 1990. p. 297–302.
- [131] Ratner BD. Surface characterization of biomaterials by electron spectroscopy for chemical analysis. *Ann Biomed Eng* 1983;11:313–36.
- [132] Baro AM, Garcia N, Miranda R, Vázquez L, Aparicio C, Olivé J, et al. Characterization of surface roughness in titanium dental implants measured with scanning tunneling microscopy at atmospheric pressure. *Biomaterials* 1986;7:463–6.
- [133] Moroni A, Caja VL, Egger EL, Trinchese L, Chao EY. Histomorphometry of hydroxylapatite coated and uncoated porous titanium bone implants. *Biomaterials* 1994;15:926–30.
- [134] Keller JC, Young FA, Natiella JR. Quantitative bone remodeling resulting from the use of porous dental implants. *J Biomed Mater Res* 1987;21:305–19.
- [135] Pilliar RM, Deporter DA, Watson PA, Valiquette N. Dental implant design—effect on bone remodeling. *J Biomed Mater Res* 1991;25:467–83.
- [136] Gilbert JL, Berkery CA. Electrochemical reaction to mechanical disruption of titanium oxide films. *J Dent Res* 1995;74:92–6.
- [137] Chehroudi B, Gould TRL, Brunette DM. Titanium-coated micromachined grooves of different dimensions affect epithelial and connective tissue cells differently *in vitro*. *J Biomed Mater Res* 1990;24:1206–19.
- [138] Chehroudi B, Gould TRL, Brunette DM. Effects of a grooved titanium coated implant surface on epithelial cell behavior, *in vitro* and *in vivo*. *J Biomed Mater Res* 1990;24:1067–85.
- [139] Michaels CM, Keller JC, Stanford CM, Solursh M. *In vitro* cell attachment of osteoblast-like cells to titanium. *J Dent Res* 1989;68:276 [Abstract No. 321].

- [140] Keller JC, Stanford CM, Wightman JP, Draughn RA, Zaharias R. Characterizations of titanium implant surfaces. *J Biomed Mater Res* 1994;28:939–46.
- [141] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones: toward a morphological compatibility of implants. *J Biomed Mater Eng* 1994;4:397–407.
- [142] Klokkevold PR, Nishimura RD, Adachi M, Caputo A. Osseointegration enhanced by chemical etching of the titanium surface. A torque removal study in the rabbit. *Clin Oral Implants Res* 1997;8:442–7.
- [143] Mattila RH, Laurila P, Rekola J, Gunn J, Lassila LV, Mäntylä T, et al. Bone attachment to glass-fibre-reinforced composite implant with porous surface. *Acta Biomater* 2009;5:1639–46.
- [144] Chehroudi B, Ghrebi S, Murakami H, Waterfield JD, Owen G, Brunette DM. Bone formation on rough, but not polished, subcutaneously implanted Ti surfaces is preceded by macrophage accumulation. *J Biomed Mater Res A* 2010;93:724–37.
- [145] Lossdörfer S, Schwartz Z, Wang L, Lohmann CH, Turner JD, Wieland M, et al. Microrough implant surface topographies increase osteogenesis by reducing osteoclast formation and activity. *J Biomed Mater Res* 2004;70A:361–9.
- [146] Hu H, Lin C, Lui PPY, Leng Y. Electrochemical deposition of hydroxyapatite with vinyl acetate on titanium implants. *J Biomed Mater Res* 2003;65A:24–9.
- [147] Vehof JWM, van den Dolder J, de Ruijter JE, Spauwen PHM, Jansen JA. Bone formation in CaP-coated and noncoated titanium fiber mesh. *J Biomed Mater Res* 2003;64A:417–26.
- [148] Spoerke ED, Stupp SI. Colonization of organoapatite-titanium mesh by preosteoblastic cells. *J Biomed Mater Res* 2003;67A:960–9.
- [149] Rodriguez R, Kim K, Ong JL. *In vitro* osteoblast response to anodized titanium and anodized titanium followed by hydrothermal treatment. *J Biomed Mater Res* 2003;65A:352–8.
- [150] Lu X, Leng Y. Quantitative analysis of osteoblast behavior on microgrooved hydroxyapatite and titanium substrata. *J Biomed Mater Res* 2003;66A:677–87.
- [151] Barrère F, van der Valk CM, Dalmeijer RAJ, Meijer G, van Blitterswijk CA, de Groot K, et al. Osteogenicity of octacalcium phosphate coatings applied on porous metal implants. *J Biomed Mater Res* 2003;66A:779–88.
- [152] Zhao G, Schwartz Z, Wieland M, Rupp F, Geis-Gerstorf J, Cochran DL, et al. High surface energy enhances cell response to titanium substrate microstructure. *J Biomed Mater Res* 2005;74A:49–58.
- [153] Takeuchi K, Saruwatari L, Nakamura HK, Yang J-M, Ogawa T. Enhanced intrinsic biomechanical properties of osteoblastic mineralized tissue on roughened titanium surface. *J Biomed Mater Res* 2005;72A:296–305.
- [154] Chiang CY, Chiou SH, Yang WE, Hsu M, Yung MC, Tsai ML, et al. Formation of TiO₂ nanonetwork on titanium surface increases the human cell growth. *Dent Mater* 2009;25:1022–9.
- [155] Buser D, Weber HP, Donath K, Fiorellini JP, Paquette DW, Williams RC. Soft tissue reactions to non-submerged unloaded titanium implants in beagle dogs. *J Periodontol* 1992;63:225–35.
- [156] Abrahamsson I, Berglundh T, Wennstrom J, Lindhe J. The peri-implant hard and soft tissues at different implant systems. A comparative study in the dog. *Clin Oral Implants Res* 1996;7:212–9.
- [157] Gargiulo AW, Wentz FM, Orban B. Dimensions and relations of the dentogingival junction in humans. *J Periodontol* 1961;32:261–7.

- [158] Arvidson K, Fartash B, Hilliges M, Kondell PA. Histological characteristics of peri-implant mucosa around Branemark and single-crystal sapphire implants. *Clin Oral Implants Res* 1996;7:1–10.
- [159] Berglundh T, Lindhe J, Ericsson I, Marinello CP, Liljenberg B, Thomsen P. The soft tissue barrier at implants and teeth. *Clin Oral Implants Res* 1991;2:81–90.
- [160] Eisenbarth E, Meyle J, Nachtigall W, Breme J. Influence of the surface structure of titanium materials on the adhesion of fibroblasts. *Biomaterials* 1996;17:1399–403.
- [161] Jansen JA, van der Waerden JP, van der Lubbe HB, de Groot K. Tissue response to percutaneous implants in rabbits. *J Biomed Mater Res* 1990;24:295–307.
- [162] Hormia M, Kononen M, Kivilahti J, Virtanen I. Immunolocalization of proteins specific for adherens junctions in humans gingival epithelial cells growth on differently processed titanium surfaces. *J Periodontal Res* 1991;26:491–7.
- [163] Mustafa K, Silva Lopez B, Hultenby K, Wennerberg A, Arvidson K. Attachment and proliferation of human oral fibroblasts to titanium surfaces with TiO₂ particles. A scanning electron microscopic and histomorphometric analysis. *Clin Oral Implants Res* 1998;9:195–207.
- [164] Kononen M, Hormia M, Kivilahti J, Hautaniemi J, Thesleff I. Effect of surface processing on the attachment, orientation, and proliferation of human gingival fibroblasts on titanium. *J Biomed Mater Res* 1992;26:1325–41.
- [165] Abrahamsson I, Zitzmann NU, Bergundh T, Linder E, Wennerberg A, Lindhe J. The mucosal attachment to titanium implants with different surface characteristics: an experimental study in dogs. *J Clin Periodontol* 2002;29:448–55.
- [166] Barboza EP, Caula AL, Carvalho WR. Crestal bone loss around submerged and exposed unloaded dental implants: a radiographic and microbiological descriptive study. *Implant Dent* 2002;11:162–9.
- [167] Raghoobar GM, Friberg B, Grunert I, Hobkirk JA, Tepper G, Wendelhag I. Three-year prospective multicenter study on one-stage implant surgery and early loading in the edentulous mandible. *Clin Implant Dent Relat Res* 2003;5:39–46.
- [168] Chou L, Firth JD, Uitto VJ, Brunette DM. Substratum surface topography alters cell shape and regulates fibronectin mRNA level, mRNA stability, secretion and assembly in human fibroblasts. *J Cell Sci* 1995;108:1563–73.
- [169] Uo M, Watari F, Yokoyama A, Matsuno H, Kawasaki T. Tissue reaction around metal implant observed by X-ray scanning analytical microscopy. *Biomaterials* 2001;22:677–85.
- [170] Sundgren J-E, Bodö P, Lundström I. Auger electron spectroscopic studies of the interface between human tissue and implants of titanium and stainless steel. *J Colloid Inter Sci* 1986;110:9–20.
- [171] Voggenreiter G, Leiting S, Brauer H, Leiting P, Majetschak M, Bardenheuer M, et al. Immuno-inflammatory tissue reaction to stainless-steel and titanium plates used for internal fixation of long bones. *Biomaterials* 2003;24:247–54.
- [172] Deporter D, Watson P, Pharoah M, Levy D, Todescan R. Five-to six-year results of a prospective clinical trial using the ENDOPORE dental implant and a mandibular overdenture. *Clin Oral Implants Res* 1999;10:95–102.
- [173] Buser D, Nydegger T, Oxland T, Cochran DL, Schenk RK, Hirt HP, et al. Interface shear strength of titanium implants with a sandblasted and acid-etched surface: a biomechanically study in the maxilla of miniature pigs. *J Biomed Mater Res* 1999;45:75–83.
- [174] Palmer RM, Plamer PJ, Smith BJ. A 5-year prospective study of Astra single tooth implants. *Clin Oral Implants Res* 2000;11:179–82.

- [175] Testori T, Wiseman L, Woolfe S, Porter SS. A prospective multicenter clinical study of the osseotite implant: four-years interim report. *Int J Oral Maxillofac Implants* 2001;16:193–200.
- [176] Sul Y-T. The significance of the surface properties of oxidized titanium to the bone response: special emphasis on potential biochemical bonding of oxidized titanium implant. *Biomaterials* 2003;24:3893–907.
- [177] Ishizawa H, Fujiino M, Ogino M. Mechanical and histological investigation of hydrothermally treated and untreated anodic titanium oxide films containing Ca and P. *J Biomed Mater Res* 1995;29:1459–68.
- [178] Larsson C, Emanuelsson L, Thomsen P, Ericson L, Aronsson B, Rodahl M, et al. Bone response to surface-modified titanium implants: studies on the tissue response after one year to machined and electropolished implants with different oxide thicknesses. *J Mater Sci Mater Med* 1997;8:721–9.
- [179] Skripitz R, Aspenberg P. Tensile bond between bone and titanium. *Acta Orthop Scand* 1998;69:2–6.
- [180] Fini M, Cigada A, Rondelli G, Chiesa R, Giardino R, Giavaresi G, et al. *In vitro* and *in vivo* behaviour of Ca and P-enriched anodized titanium. *Biomaterials* 1999;20:1587–94.
- [181] Henry P, Tan AE, Allan BP. Removal torque comparison of TiUnite and turned implants in the Greyhound dog mandible. *Appl Osseoint Res* 2000;1:15–7.
- [182] Sul Y-T, Johansson CB, Jeong Y, Wennerberg A, Albrektsson T. Resonance frequency and removal torque analysis of implants with turned and anodized surface oxide. *Clin Oral Implants Res* 2002;13:252–9.
- [183] Sul Y-T, Johansson CB, Jeong Y, Röser K, Wennerberg A, Albrektsson T. Oxidized implants and their influence on the bone response. *J Mater Sci Mater Med* 2001;12:1025–31.
- [184] Sul Y-T, Johansson CB, Albrektsson T. Oxidized titanium screws coated with calcium ions and their performance in rabbit bone. *Int J Oral Maxillofac Implants* 2002;17:625–34.
- [185] Lim YJ, Oshida Y, Andres CJ, Barco MT. Surface characterizations of variously treated titanium materials. *Int J Oral Maxillofac Implants* 2001;16:333–42.
- [186] Meachim G, Williams DF. Changes in nonosseous tissue adjacent to titanium implants. *J Biomed Mater Res* 1973;7:555–71.
- [187] Albrektsson T, Jacobsson M. Bone–metal interface in osseointegration. *J Prosthet Dent* 1987;57:5–10.
- [188] Lausmaa J. Chemical composition and morphology of titanium surface oxides. *Mat Res Soc Symp Proc* 1986;55:351–9.
- [189] Kohavi D, Schwartz Z, Amir D, Muller Mai C, Gross U, Sela J. Effect of titanium implants on primary mineralization following 6 and 14 days of rat tibial healing. *Biomaterials* 1992;13:255–60.
- [190] Jasty M, Bragdon CR, Haire T, Mulroy RD, Harris WH. Comparison of bone ingrowth into cobalt chrome sphere and titanium fiber mesh porous coated cementless canine acetabular components. *J. Biomed Mater Res* 1993;27:639–44.
- [191] Hazan R, Brener R, Oron U. Bone growth to metal implants is regulated by their surface chemical properties. *Biomaterials* 1993;14:570–4.
- [192] Changd YS, Oka M, Kobayashi M, Gu HO, Li ZL, Nakamura T, et al. Significance of interstitial bone ingrowth under load-bearing conditions: a comparison between solid and porous implant materials. *Biomaterials* 1996;17:1141–8.

- [193] Piattelli A, Corigliano M, Scarano A. Microscopical observations of the osseous responses in early loaded human titanium implants: a report of two cases. *Biomaterials* 1996;17:1333–7.
- [194] Goodman S, Aspenberg P. Effect of amplitude of micromotion on bone ongrowth into titanium chambers implanted in the rabbit tibia. *Biomaterials* 1992;13:944–8.
- [195] Li J, Liao H, Fartash B, Hermansson L, Johnsson T. Surface-dimpled commercially pure titanium implant and bone ingrowth. *Biomaterials* 1997;18:691–6.
- [196] French AA, Bowles CQ, Parharn PL, Eick JD, Killoy WJ, Cobb CM. Comparison of peri-implant stresses transmitted by four commercially available osseointegrated implants. *Int J Periodont Rest Dent* 1989;9:221–30.
- [197] Bidez MW, Misch CE. Force transfer in implant dentistry. Basic concepts and principles. *J Oral Implantol* 1992;18:264–74.
- [198] Adell R, Lekholm U, Rockler B, Brånemark P-IA. 15-year study of osseointegrated implants in the treatment of the edentulous jaws. *Int J Oral Surg* 1981;10:387–416.
- [199] Schliephake H, Scharnweber D, Dard M, Rößler S, Sewing A, Hüttmann C. Biological performance of biomimetic calcium phosphate coating of titanium implants in the dog mandible. *J Biomed Mater Res* 2003;64A:225–34.
- [200] Groessner-Schreiber B, Neubert A, Müller W-D, Hopp M, Griepentrog M, Lange KP. Fibroblast growth on surface-modified dental implants: an *in vitro* study. *J Biomed Mater Res* 2003;64A:591–9.
- [201] Vasudev DP, Ricci JL, Sabatino C, Li P, Parsons JR. *In vivo* evaluation of a biomimetic apatite coating grown on titanium surfaces. *J Biomed Mater Res* 2004; 69A:629–36.
- [202] Knabe C, Howlett CR, Klar F, Zreiqat H. The effect of different titanium and hydroxyapatite-coated dental implant surfaces on phenotypic expression of human bone-derived cells. *J Biomed Mater Res* 2004;71A:98–107.
- [203] Lu X, Leng Y, Zhang X, Xu J, Qin L, Chan C-W. Comparative study of osteoconduction on micromachined and alkali-treated titanium alloy surfaces *in vitro* and *in vivo*. *Biomaterials* 2005;26:1793–801.
- [204] Elmengaard B, Bechtold JE, Søballe K. *In vivo* effects of RGD-coated titanium implants inserted in two bone-gap models. *J Biomed Mater Res* 2005;75A:249–55.
- [205] Elmengaard B, Bechtold JE, Søballe K. *In vivo* study of the effect of RGD treatment on bone ongrowth on press-fit titanium alloy implants. *Biomaterials* 2005;26:3521–6.
- [206] Uo M, Asakura K, Yokoyama A, Ishikawa M, Tamura K, Totsuka Y, et al. X-ray absorption fine structure analysis of titanium-implanted soft tissue. *Dent Mater J* 2007;26:268–73.
- [207] Chen GJ, Wang Z, Bai H, Li JM, Cai H. A preliminary study on investigating the attachment of soft tissue onto micro-arc oxidized titanium alloy implants. *Biomed Mater* 2009;4:015017.
- [208] Bothe RT, Beaton LE, Davenport HA. Reaction of bone to multiple metallic implants. *Surg Gynecol Obstet* 1940;71:598–602.
- [209] Brånemark P-I, Hansson BO, Adell R, Briene U, Lindstrom J, Hallen O, et al. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scand J Plast Reconstr Surg Suppl* 1977;16:1–132.
- [210] Misch CE, Misch CM. Generic root form component terminology. In: Misch CE, editor. *Implant dentistry*. St. Louis, MO: Mosby, an Affiliate of Elsevier; 1999. p. 13–5.
- [211] Brånemark R, Brånemark P-I, Rydevik B, Myers RR. Osseointegration in skeletal reconstruction and rehabilitation. *J Rehabil Res Dev* 2001;38:175–82.

- [121] Zaffe D, Baena RR, Rizzo S, Brusotti C, Soncini M, Pietrabissa R, et al. Behavior of the bone–titanium interface after push-in testing: a morphological study. *J Biomed Mater Res* 2003;64A:365–71.
- [122] Rønold HJ, Lyngstadaas SP, Ellingsen JE. A study on the effect of dual blasting with TiO₂ on titanium implant surfaces on functional attachment in bone. *J Biomed Mater Res* 2003;67A:524–30.
- [123] Nishiguchi S, Fujibayashi S, Kim H-M, Kokubo T, Nakamura T. Biology of alkali- and heat-treated titanium implants. *J Biomed Mater Res* 2003;67A:26–35.
- [124] Giavaresi G, Fini M, Cigada A, Chiesa R, Rondelli G, Rimondini L, et al. Histomorphometric and microhardness assessments of sheep cortical bone surrounding titanium implants with different surface treatments. *J Biomed Mater Res* 2003;67A:112–20.
- [125] Fujibayashi S, Neo M, Kim HM, Kokubo T, Namamura T. Osteoinduction of porous bioactive titanium metal. *Biomaterials* 2004;25:443–50.
- [126] Takemoto M, Fujubayashi S, Neo M, Suzuki J, Kokubo T, Nakamura T. Mechanical properties and osteoinductivity of porous bioactive titanium. *Biomaterials* 2005;26:6014–23.
- [127] Takemoto M, Fujibayashi S, Neo M, Suzuki J, Matsushita T, Kokubo T, et al. Osteoinductive porous titanium implants: effect of sodium removal by dilute HCl treatment. *Biomaterials* 2006;27:2682–91.
- [128] Sul Y-T, Johansson C, Byon E, Albrektsson T. The bone response of oxidized bioactive and non-bioactive titanium implants. *Biomaterials* 2005;26:6720–30.
- [129] Aebli N, Krebs J, Stich H, Schawalder P, Walton M, Schwenke D, et al. *In vivo* comparison of the osseointegration of vacuum plasma sprayed titanium- and hydroxyapatite-coated implants. *J Biomed Mater Res* 2003;66A:356–63.
- [130] Stewart M, Welter JF, Goldberg VM. Effect of hydroxyapatite/tricalcium-phosphate coating on osseointegration of plasma-sprayed titanium alloy implants. *J Biomed Mater Res* 2004;69A:1–10.
- [131] Habibovic P, Li J, van der Valk CM, Meijer G, Layrolle P, van Blitterswijk CACA, et al. Biological performance of uncoated and octacalcium phosphate-coated Ti6Al4V. *Biomaterials* 2005;26:23–36.
- [132] Stangl R, Pries A, Loos B, Müller M, Erben RG. Influence of pores created by laser superfinishing on osseointegration of titanium alloy implants. *J Biomed Mater Res* 2004;69A:444–53.
- [133] Götz HE, Müller M, Emmel A, Holzwarth U, Erben RG, Stangl R. Effect of surface finish on the osseointegration of laser-treated titanium alloy implants. *Biomaterials* 2004;25:4057–64.
- [134] Giannuzzi LA, Phifer D, Giannuzzi NJ, Capuano MJ. Two-dimensional analysis of bone–dental implant interfaces with the use of focused ion beam and electron microscopy. *J Oral Maxillofac Surg* 2007;65:737–47.
- [135] Stenport VF, Jphansson CB. Evaluations of bone tissue integration to pure and alloyed titanium implants. *Clin Implant Dent Relat Res* 2008;10:191–9.
- [136] Morinaga K, Kido H, Sato A, Watazu A, Matsuura M. Chronological changes in the ultrastructure of titanium–bone interfaces: analysis by light microscopy, transmission electron microscopy, and micro-computed tomography. *Clin Implant Dent Relat Res* 2009;11:59–68.
- [137] Kerner S, Mogonney V, Pavon-Djavid G, Helay G, Sedel L, Anagnostou F. Bone tissue response to titanium implant surfaces modified with carboxylate and sulfonate groups. *J Mater Sci Mater Med* 2010;21:707–15.

- [229] Fujishiro T, Nishikawa T, Shibamura N, Akisue T, Takikawa S, Yamamoto T, et al. Effect of cyclic mechanical stretch and titanium particles on prostaglandin E₂ production by human macrophages *in vitro*. J Biomed Mater Res 2004;68A:531–6.
- [230] Lin H-Y, Bumgardner JD. *In vitro* biocorrosion of Ti–6Al–4V implant alloy by a mouse macrophage cell line. J Biomed Mater Res 2004;68A:717–24.
- [231] Sommer B, Felix R, Sprecher C, Leunig M, Ganz R, Hofstetter W. Wear particles and surface topographies are modulators of osteoclastogenesis *in vitro*. J Biomed Mater Res 2005;72A:67–76.
- [232] Tjellström A. Osseointegrated systems and their applications in the head and neck. Adv Otolaryngol Head Neck Surg 1989;3:39–70.
- [233] Granström G. Osseointegration in irradiated cancer patients. An analysis with respect to implant failures. J Oral Maxillofac Surg 2005;63:579–85.
- [234] Treccani L, Maiwald M, Zöllmer V, Busse M, Grathwohl G, Rezwan K. Antibacterial and abrasion-resistant alumina micropatterns. Adv Eng Mater 2009;11:B61–6.
- [235] Lin Y-S, Burggraaf AJ. Preparation and characterization of high-temperature thermally stable alumina composite membrane. J Am Ceram Soc 1991;74:219–24.
- [236] Liu Y, Chen OY, Wei CC, Li K. Preparation of yttria-stabilised zirconia (YSZ) hollow fibre membranes. Desalination 2006;199:360–2.
- [237] Wenz HJ, Bartsch J, Wolfart S, Kern M. Osseointegration and clinical success of zirconia dental implants: a systematic review. Int J Prosthodont 2008;21(1):27–36.
- [238] Fernández-Fairén M, Sala P, Gil FJ. Failures of yttria-stabilised tetragonal zirconia: 52 retrieved ceramic femoral heads of total hip prostheses. Biomed Mater Eng 2006;16:415–22.
- [239] Schincaglia GP, Marzola R, Scapoli C, Scotti R. Immediate loading of dental implants supporting fixed partial dentures in the posterior mandible: a randomized controlled split-mouth study: machined versus titanium oxide implant surfaces. Int J Oral Maxillofac Implants 2007;22:35–46.
- [240] Domanski M, Winnubst L, Luttge R, Lamers E, Walboomers XF, Jansen J, et al. Production and characterization of micro- and nanofeatures in biomedical alumina and zirconia ceramics using a tape casting route. J Mater Sci Mater Med 2012;23:1637–44.

This page intentionally left blank

8 Implant Application

8.1 Introduction

In the past, a metallic post was either cemented or screwed into the canals of teeth that had lost their crowns but still had their roots. Such teeth are “root treated” to remove their nerves and blood supplies, and onto the posts ceramic or ceramic metal crowns are themselves cemented. Although many attempts have been made to replace missing roots with all sorts of metallic implants, the satisfactory use of a screwed-in implant was found only in the mid-1980s. In practice, the gum is slit and a hole is cut slowly in the bone, and then a CpTi screw is slowly inserted and covered with gum tissue for six months. During this time, the bone grows into intimate contact with the passive oxide layer on the titanium and it is said to be osteointegrated. The gum tissue is cut once more, and a titanium sleeve is screwed onto the implant. This will ultimately pass through the healed gum. Onto these sleeves a metallic superstructure can be screwed, and this can support, for example, a polymeric denture base and artificial teeth. For many years, these superstructures have been cast in gold alloys and getting them to sit perfectly on the titanium sleeves has been a challenge of the highest order. However, titanium frameworks are currently being investigated, particularly those constructed by alternative routes to casting, and considerable promise is being shown by those made by superplastic forming. Titanium implants, for example, have had their surfaces coated with hydroxyapatite to promote the osteointegration [1].

The service conditions in the mouth are hostile, both corrosively and mechanically. All parts are continuously bathed in saliva, an aerated aqueous solution of about 0.1 N chloride ion, with varying amounts of Na, K, Ca, PO_4 , CO_2 , sulfur compounds, and mucin. The pH value is normally in the range from 5.5 to 7.5, but under plaque deposits it can be as low as pH 2. Temperatures can vary $\pm 36.5^\circ\text{C}$, and a variety of food and drink concentrations (in both acid and alkaline) apply for short periods. Loads may be up to 1000 N, sometimes at impact speeds. Trapped food debris may decompose and sulfuric compounds discolor [2].

Direct bony interface promised more predictability and longevity than previously used systems; hence, oral implantology gained significant additional momentum. A carefully planned full rehabilitation of the mouth using “state-of-the-art” methods can free the patient from dental problems for decades. However, this can only be achieved with the complete cooperation of the patient, accompanied by regular supervision and care on the part of the dental surgeon and his assistants (for

example, the dental hygienist). Accordingly, there are four major factors which should be met to accomplish the successful implant: (1) correct indication and favorable anatomic conditions (bone and mucosa), (2) good operative technique, (3) patient cooperation (oral hygiene), and (4) adequate superstructure. In 2000, Binon [3] had reported that there are approximately 25 dental implants manufacturing companies producing about 100 different dental implant systems with a variety of diameters, lengths, surfaces, platforms, interfaces, and body designs. Currently (year 2012), there are approximately 130–150 implant (only oral) companies; hence, intraoral implant systems should be around 300–500 systems [4]. Even with the huge variety of implants currently available, the most logical differentiations and distinctions are simply based on the implant/abutment interface, the body shape, and the implant-to-bone surface.

There are two ways to retain the implant restorations: cementation and screw tightening. Implant superstructures are usually made by the lost-wax casting method and are normally gold alloy beams that fit directly onto metallic components called abutments that protrude through the soft tissues of the mouth and which are themselves attached to machined titanium components known as dental implants. The dental implants are placed in the hard bone tissues where intimate contact occurs between the metallic component and the natural tissues. The superstructure is screwed or cemented to the abutments, and teeth are then placed along the beam in an esthetic fashion. Patients prefer this form of fixed bridgework as it is more reminiscent of their natural teeth than a denture. For the whole prosthesis to have the optimal chance of success, there must be no misfit between the beam and the abutments. Mainstream philosophy in the design and restoration of implant prostheses from the 1980s through the early 1990s reflected a strong preference for screw-retained over cement-retained restorations. This preference most likely was the result of how osteointegrated implants and their restoration were introduced. Although retrievability remains the primary advantage of a screw-retained approach, cemented implant restorations are attractive for several reasons. First, the preclusion of the interference of screw access holes with esthetic results or with the occlusion of the restoration. Second, cement-retained approaches substantially reduce restoration costs. With some systems, screw-retained restoration involves nearly four times the component cost of cemented restoration. Third, if no occlusal screw is present, occlusal screw loosening is not a possible complication of implant prosthodontics. Fourth, a cemented restoration is more likely to achieve passive fit than a screw-retained restoration. The argument for increased passivity rests on the assumption that tightening a screw-retained restoration may create substantial strain within the restoration, implant, and investing bone complex. The use of cemented restorations also avoids the clamping effect of multiple screws drawing an ill-fitting prosthesis into place against the support. Fifth, the implant industry's desire to extend routine implant use into the general dental practices has stimulated interest in simplifying implant restorative procedures. Cementation of fixed implant restorations more closely follow the procedures routinely performed on natural teeth [5,6].

The implantation of devices for the maintenance or restoration of a body function imposes extraordinary requirements on the materials of construction. Foremost

among these is an issue of biocompatibility, as discussed earlier in Chapters 6 and 7. There are interactions between the material and the surrounding living tissue, fluid, and blood elements. Some of these are simply adaptive. Others constitute hazards, both short and long term, to the survival of the living system [3,7–10]. There are mechanical and physical properties which the material must provide. Some of these govern the ability of the device to provide its intended function from a purely engineering viewpoint. Others such as tribology including wear and friction, corrosion and mechanical compliance relate significantly to the biocompatibility issue. Human implantation applications impose more stringent requirements on reliability than any other engineering task. In most applications, an implanted device is expected to function for the life of the patient. It is necessary to think in terms of reliability of performance of thousands of devices for the lifetime of a patient and a tolerable expectation of failure of perhaps no more than one in one thousand. Most available data in handbooks, publications, and product brochures represent mean values and supplementary statistical information, and, therefore, comparable reliability is also in question [8–10]. However, it is surprising to note that there is no safety factor concept in the dental and medical area, whereas it is a very important concept in engineering, particularly designing crucial structures and structural components.

As for orthopedic implants, natural synovial joints, e.g., hip, knee, or shoulder joints, are complex and delicate structures capable of functioning under critical conditions. Unfortunately, human joints are prone to degenerative and inflammatory diseases that result in pain and joint stiffness. Primary or secondary osteoarthritis (osteoarthrosis) and to a lesser extent rheumatoid arthritis (inflammation of the synovial membrane) and chondromalacia (softening of cartilage) are, apart from normal aging of articular cartilage, the most common degenerative processes affecting synovial joints. In fact, 90% of the population over the age of 40 suffers from some degree of degenerative joint disease. Premature joint degeneration may arise from deficiencies in joint biomaterial properties, from excessive loading conditions, or from failure of normal repair processes, where the explicit degenerative processes are not yet completely understood <http://www.jointpainremedy.com> [11].

The use of Ti materials for medical and dental implant applications has increased tremendously over the past few decades. One of the prime reasons for this increased use is the design of implants around its unique properties. In the case of high load bearing and fatigues, for devices such as hip prostheses, Ti should be the metal of choice because of its combination of strength, corrosion resistance, light weight, good biotribological property, and biocompatibility. Advances in Ti materials development, casting technology, and powder metallurgy (P/M) will offer benefits to both the surgeon and the patient. Casting of Ti alloys has arrived as a technology that can be utilized by the implant industry. Hip prostheses made from cast and hot isostatically pressed (HIPed) Ti–6Al–4V are currently being used. Advanced P/M—metal injection molding (MIM)—can be used to fabricate a whole implant body or surface layer of them. The P/M along with MIM exhibits a remarkable advantage over the conventional casting, since the highest process temperature is within the solid state (diffusion) opposed to the melting process involved in casting process. Owing to

these benefits, almost every possible alloying combination can be achieved. In addition to these technologies, the idea of using superplastic forming started when a dental practitioner was looking for a method of producing dental implant superstructures with a passive fit [12,13] (Chapter 10).

Traditionally, the majority of geriatric dental services for the elderly have been provided to healthy, independent, older adults requiring few special considerations other than normal physiologic age-related changes and their potential impact on the oral cavity. This is no longer an acceptable approach. Over 80% of the geriatric population has at least one chronic disease, and many elderly have several such conditions simultaneously. The rapid growth of the elderly population will have a dramatic impact on the practice of dentistry [14]. In 1984, 27.9 million, or one in nine, adults in the US were 65 years of age or older. It is anticipated that those over 65 will account for 70.2 million people, or 20% of the US population, by the year 2030 [15]. It was mentioned that (1) age should not exclude patients from implant treatment, (2) dental implants and implant-retained and/or -supported prostheses are valuable treatment options for geriatric patients, (3) early implant intervention is strongly recommended when the patient feels able and is willing to undergo dental and prosthetic therapy, (4) diminished levels of oral hygiene that often accompany aging are not a contraindication to implant treatment, and (5) clinicians should be aware of potential risks, possible medical complications, and psychosocial issues in geriatric patients, and how these conditions can affect the implant prognosis [14].

There are at least three major required compatibilities for placed implants to exhibit biointegration to receive hard tissue and biofunctionality thereafter. They include (1) biological compatibility (in other words, biocompatibility), (2) mechanical compatibility (or mechanocompatibility), and (3) morphological compatibility [16,17]. One of many universal requirements of implants, wherever they are used in the body, is the ability to form a suitably stable mechanical unit with the neighboring hard or soft tissues. A loose (or unstable) implant may function less efficiently or cease functioning completely, or it may induce an excessive tissue response. In either case, it may cause the patient discomfort and pain. In several situations, a loose implant was deemed to have failed and needed to be surgically removed. For a long time it has been recognized that any type of implant (for both dental implants and orthopedic implants) should possess a biological compatibility against an implant receiving surrounding hard/soft tissues. Accordingly, the material choice for implants is limited to certain types of materials, including titanium materials, stainless steels, or some ceramic materials. The dental or orthopedic prostheses, and particularly the surface zones thereof, should respond to the loading transmitting function. The placed implant and receiving tissues establish a unique stress-strain field. Between them, there should be an interfacial layer. During the loading, the strain field continuity should be held, although the stress field is obviously in a discrete manner due to different values of modulus of elasticity (MOE) between host tissue and foreign implant material. If the magnitude of the difference in MOE is large, then the interfacial stress, accordingly, will be so large that the placed implant system will face a risky failure situation. Therefore, materials for

implant or surface zones of implants should be mechanically compatible with the mechanical properties of the receiving tissues so that the interfacial discrete stress can be minimized. This is the second compatibility and is called as the mechanical compatibility. In a scientific article [17], it was found that surface morphology of successful implants has upper and lower limitations in average roughness (1–50 μm) [16,17] (Figure 7.1) and average particle size (10–500 μm) [16,17], regardless of the type of implant material (metallic, ceramics, or polymeric materials). If a particle size is smaller than 10 μm , the surface will be more toxic to fibroblastic cells and have an adverse influence on cells due to their physical presence independent of any chemical toxic effects. If the pore is larger than 500 μm , the surface does not maintain sufficient structural integrity because it is too coarse. This is the third compatibility—morphological compatibility [16,17].

The criteria for clinical success of osteointegration and the conditions of functional compatibility are dependent on the control of several factors including (1) biocompatible implant material using commercially pure titanium, (2) design of the fixture: a threaded design is advocated, creating a larger surface per unit volume as well as evenly distributing loading forces, (3) the provision of optimal prosthodontic design and implant maintenance to achieve ongoing osteointegration, (4) a specific aseptic surgical technique and a subsequent healing protocol that are reconcilable with the principles of bone physiology; this would incorporate a low-heat/low-trauma regimen, a precise fit and the two-stage surgery program, (5) a favorable status of host–implant site from a health and morphologic standpoint, (6) nonloading of the implant during healing as the basic principle for successful osteointegration, and (7) the defined macro/microscopic surface of the implant as it relates to the host tissue [18].

8.2 Intraoral Implants Versus Extraoral Implants

Since Brånemark introduced the concept of osteointegration over three decades ago, dental implants have been widely used to replace teeth and, more importantly, to retain or support intra- and extraoral prostheses [19,20]. While intraoral dental implants are well developed and thoroughly studied, this is not the case for the extraoral implants. Intraoral implants should include dental implants and all types of orthopedic implants (such knee, hip, shoulder, hand, and foot joint replacements). There are only a handful of longitudinal studies for extraoral implants. These studies, along with several case reports, suggest that the success criteria and complications of extraoral implants are unique to the implant sites. For instance, auricular implants have a survival rate close to 100%. However, the success rates were only about 75–90% for nasal and orbital implants [21–23]. Not only does the uniqueness of anatomic structures affect the survival rate of the extraoral implants, but oftentimes the maxillofacial patients lose anatomical structure from surgical resection and may also undergo chemotherapy or radiation therapy. These preprosthetic treatments can further compromise the survival of the implants and increase complications. In addition to this, the extraoral environment seems to predispose the implants to soft tissue

infection that is distinct from the intraoral implants, where it is rare to have similar soft tissue complication [20,24]. The improvement of surgical techniques, postoperation care, and prosthetic fabrication may have improved the implant survival rate and reduced complications [20,23,25].

The extraoral implants should also include percutaneous implants used for head and neck reconstruction [26]. Such craniofacial osseointegration can be applied to fabricate various types of extraoral implants and prostheses, including otorhinolaryngology (ENT) implants such as bone-anchored hearing aids, bone-anchored epistheses, orbit prosthetics, nose prosthetics, and midface prosthetics [19,27–30].

The concept of anchoring craniofacial prostheses on osteointegrated implants was accepted by the Food and Drug Administration (FDA) in 1985 and FDA accepted the concept of anchored hearing aids in adults in 1995 and in children in 1998 [31].

There are several areas of development that appear important to the future of extraoral osseointegration and its application to facial prosthetics. A challenge remaining is that the soft tissues do not attach to the percutaneous abutment [26]. Advanced manufacturing technologies will become increasingly important to this field of endeavor, including color matching to skin color [32,33].

8.3 Clinical Reports

Before we go into further detail reviewing surface characterization and implant reactions in various environments, it would be worthwhile to know what is actually happening in clinical fields. Although, as we will observe later, dental implants are enjoying their success rates, there is still much research to be done. This initiative will encourage clinical research on osteointegrated dental implants regarding (1) outcomes when using various surgical and prosthetic protocols (e.g., immediate placement versus delayed placement; implant placement following osseous grafting and/or sinus augmentation; immediate versus delayed prosthetic loading), (2) the role of systemic diseases in the success rate of osteointegrated implants, (3) quality of life and patient preferences for dental implants compared to other prosthetic methods for restoring the dentition, and (4) needs in children who have congenitally missing teeth or suffer from developmental disabilities. Osteointegrated dental implants are one of the options available for replacing missing teeth. The success of implants has been attributed to osteointegration or direct contact of the implant surface and bone without a fibrous connective tissue interface. Varying surgical protocols are used for placement of implants, and a wide variety of implant designs are in current use. Implant failure is reported to be higher in smokers than in non-smokers. It is obvious that smoking is one of the contraindications for receiving dental implants, as discussed in Chapter 7. While there are reports of similar failure rates between people with well-controlled diabetes and those without diabetes, individuals with Type 2 diabetes may have a slightly higher failure rate. No studies have documented the success of implants in individuals who develop diabetes, osteoporosis, or other systemic conditions after placement. In general, the relationship between systemic health and implant success is not well documented. The use of

surgical procedures such as maxillary sinus lifts, inferior alveolar nerve transposition, and guided bone regeneration have expanded the use of implants [34]. Adell et al. [34] reported the clinical review on the long-term outcome of prostheses and fixtures (titanium implants) in 759 totally edentulous jaws of 700 patients. A total of 4636 standard implants were placed and followed according to the osteointegration method for a maximum of 24 years by the original team at the University of Göteborg. Standardized annual clinical and radiographic examinations were conducted as far as possible. A life-table approach was applied for statistical analysis. Sufficient numbers of implants and prostheses for a detailed statistical analysis were present for observation times up to 15 years. More than 95% of maxillae had continuous prosthesis stability at 5 and 10 years and at least 92% at 15 years. The figure for mandibles was 99% at all time intervals. Calculated from the time of implant placement, the estimated survival rates for individual implants in the maxilla were 84%, 89%, and 92% at 5 years; 81% and 82% at 10 years; and 78% at 15 years. In the mandible, they were 91%, 98%, and 99% at 5 years; 89% and 90% at 10 years; and 86% at 15 years [34,35].

Åstrand et al. [36] reported the following clinical studies. Twenty-three patients with Kennedy Class I mandibular dentition were supplied with prostheses in the posterior parts of the mandible. On one side they were given a prosthesis supported by two implants (Type I) and on the other side they received a prosthesis supported by one implant and one natural tooth (Type II). A total of 69 fixtures (titanium implants) were inserted and 46 prostheses constructed. Eight of the implants were lost during the observation period. The failure rate of the implants was about the same in the two types of prostheses: 5 implants belonged to prostheses type I (10.9%) and 2 implants belonged to prostheses type II (8.7%), while one implant was lost prior to loading. From a theoretical point of view, the combination of a tooth and an osteointegrated implant should encounter problems with regard to the difference in bone anchorage, and there should be a risk of biomechanical complications. However, the results of this study did not indicate any disadvantages in connecting teeth and titanium implants in the same restoration [36].

The structural and functional bonding of load-carrying titanium implants to living bone has been recognized, indicating that the implant was successfully accepted. The effect of CpTi implants on the process of primary mineralization was studied by Kohavi et al. [37] by insertion of Ti implants into rat bone after ablation. The effects of the Ti were studied through the behavior of extracellular matrix vesicles. It was found that (i) the insertion of Ti implants was followed by an increase in the number of extracellular matrix vesicles as well as vesicular diameter, and by a decrease in vesicular distance from the calcified front when compared to normal healing, suggesting that the process of extracellular matrix vesicles maturation around Ti implants was delayed when compared to normal primary bone formation during bone healing and (ii) the delay in mineralization was compensated by an increase in vesicular production, resulting in an enhancement of primary mineralization by the titanium [37]. Piattelli et al. [38] reported on the histological picture of the surrounding two screw-shaped Ti plasma-sprayed implants retrieved for a fracture of the abutment after 18 and 42 months. These two

implants were loaded after 2 months. The microscopic examination showed that both implants were covered in a large part of the implant surface by compact, mature lamellar bone with the presence of many Haversian systems, and osteons. With von Kossa staining, it was possible to see that the bone at the interface with the implant was highly mineralized. No connective tissue or inflammatory cells were present at the interface [38].

Saadoun and Le Gall [39] presented the 8-year study showing an increased success rate for Steri-Oss osteointegrated implants in full, partial, and single-tooth edentation compared to the previous 6-year studies. A total of 1499 titanium implants placed in 389 women and 216 men had an average success rate of 96.1%. Of the 716 implants placed in the maxilla, 697 were exposed and only 31 failed—a success rate of 95.6%. Of 783 placed in the mandible, 750 were exposed and 25 failed—a success rate of 96%. Performance comparisons of Steri-Oss Ti threaded, HA-coated cylindrical implants and Ti plasma-sprayed cylindrical implants showed a higher success rate for the coated and sprayed implants, especially for short implants placed in soft maxillary bone [39].

A histological analysis of 19 Brånemark titanium implants retrieved for different causes was reported: (1) four implants were removed for abutment fracture, (2) one for dental nerve dysesthesia, (3) two for bone overheating, (4) two for periimplantitis, (5) nine for mobility, and (6) one for unknown causes. It was mentioned that, in the implants removed for fracture, a high-bone–implant contact percentage was present (72%), with compact, mature bone at the interface. It was also reported that, in periimplantitis, an inflammatory infiltrate was observed in the preimplant tissues: a dense fibrous connective tissue was present around implants failed because of its mobility [40].

Successful endosseous implant therapy requires integration of the implant with bone, soft connective tissue, and epithelium. There were several important observations made by Cochran [41] and are as follows. Light and electron microscopy reveal that epithelial structures similar to teeth are found around the implants. A connective tissue zone exists between the apical extension of the junctional epithelium and the alveolar bone. This connective tissue comprises a dense circular avascular zone of connective tissue fibers surrounded by a loose vascular connective tissue. The histological dimensions of the epithelium and connective tissue comprising the biologic width are similar to the same tissues around teeth. Straumann titanium implants have an endosseous portion that is either coated with a well-characterized and -documented titanium plasma-sprayed surface or is sand blasted and acid etched. Both surfaces have been shown to have advantages for osseous integration compared to as-machined and other smoother implant surfaces, as we saw in Chapter 7. These advantages include greater amounts of bone-to-implant contact (mechanical anchorage), more rapid integration with bone tissue (biochemical anchorage), and higher removal torque values (as a result of both). Component connection at the alveolar crest, as seen with submerged implants, results in microbial contamination, crestal bone loss, and a more apical epithelial location [41].

Leonhardt et al. [42] followed up longitudinally osteointegrated titanium implants in partially dentate patients by clinical, radiographic, and microbiological parameters

in order to evaluate possible changes in the periimplant health over time. Fifteen individuals treated with titanium implants and followed for 10 years were included in the study. Before implant placement 10 years prior, the individuals had been treated for advanced periodontal disease and thereafter been included in a maintenance care program. The survival rate of the implants after 10 years was 94.7%. Of the individuals, 50% were positive for plaque at the implants. Bleeding on sulcus probing was present at 61% of the implant surfaces. The results of the present study suggest that the presence of these putative periodontal pathogens at implants may not be associated with an impaired implant treatment. These species are most likely part of the normal resident microbiota of most individuals and may therefore be found at random at both stable and progressing periimplant sites [42].

ITI® dental implants are available with two bone-anchoring surfaces: a titanium plasma-sprayed surface, and a recently introduced sand-blasted and acid-etched surface. Cell culture and animal tests demonstrate that the sand-blasted and acid-etched surface stimulates bone cell differentiation and protein production, has large amounts of bone-to-implant contact, and results in large removal torque values in functional testing of the bone contact. The 5-year follow-up revealed that 110 patients with 326 implants have completed the 1-year postloading recall visit, while 47 patients with 138 implants have completed the 2-year recall. Three implants were lost prior to abutment connection. Prosthetic restoration was commenced after shortened healing times on 307 implants. The success rate for these implants, as judged by abutment placement, was 99.3% (with an average healing time of 49 days). It was further analyzed by the life-table analyses that there was an implant success rate of 99.1%, both for 329 implants at 1 year and for 138 implants at 2 years. It was also reported that, under defined conditions, solid screw implants with a sand-blasted and acid-etched endosseous surface can be restored after approximately 6 weeks of healing with a high predictability of success, defined by abutment placement at 35 N cm without counter-torque and 2 years after restoration with subsequent implant success rates of greater than 99% [43].

Meijer et al. [44] conducted the prospective randomized controlled clinical trial to evaluate the clinical outcomes and prosthetic aftercare of edentulous patients with a mandibular overdenture retained by two IMZ titanium implants or two Brånemark titanium implants during a 10-year period. Patients were allocated to the IMZ group ($n = 29$) or the Brånemark group ($n = 32$). In the IMZ group, four implants were lost during the 10-year follow-up (survival rate: 93%). In the Brånemark group, nine implants were lost (survival rate: 86%). All patients were reoperated successfully. Multiple prosthetic revisions were necessary in both groups. In particular, the precision attachment system in the overdenture (23% of the total number of revisions) and the denture base and teeth (26% of the total number of revisions) were subject to frequent fracture. It was concluded that both the IMZ implant and the Brånemark implant systems supporting an overdenture are functioning well after 10 years of follow-up. There are no indications of a worsening of clinical or radiographical state after 10 years [44].

Ichinose et al. [45] demonstrated that a myriad of fine particles produced by the abrasion of both Co–Cr–Mo and Ti–6Al–4V alloys accumulate in the synovial

cells next to surgical implants made from these alloys. The metallic particles were of various sizes and were observed within the lysosomes. Energy dispersive X-ray spectroscopy studies revealed that the fine spherical particles consisted solely of Cr and that other larger particles were composed of the Co–Cr–Mo alloy. It was reported that most of the fine particles were 10–15 nm in diameter, and 80% of the large particles were 30–35 nm in length and 20–25 nm in width. In addition, the energy dispersive X-ray spectroscopy analysis clarified that all of the fine particles of the Ti–6Al–4V were composed of that alloy. For Ti–6Al–4V, when discounting the large particles, the fine metal deposits were 20–25 nm in length and 10–15 nm in width. It was concluded that (i) Co–Cr–Mo alloy is easily corroded and that Co is released from the cells and (ii) Ti–6Al–4V alloy is very stable and does not corrode, although the Ti–6Al–4V alloy does produce particles that are smaller than those produced by the Co–Cr–Mo alloy [45].

Goodacre et al. [46] reviewed articles to identify the types of complications that have been reported in conjunction with endosseous root form implants and associated implant prostheses. The searches focused on Medline publications (which started in 1981) that contained clinical data regarding success/failure/complications. The complications were divided into the following six categories: surgical, implant loss, bone loss, periimplant soft tissue, mechanical, and esthetic/phonetic. The raw data were combined from multiple studies and means calculated to identify trends noted in the incidences of complications. It was reported that the most common implant complications (those with greater than a 15% incidence) were loosening of the overdenture retentive mechanism (33%), implant loss in irradiated maxillae (25%), hemorrhage-related complications (24%), resin veneer fracture with fixed partial dentures (22%), implant loss with maxillary overdentures (21%), overdentures needing to be relined (19%), implant loss in type IV bone (16%), and overdenture clip/attachment fracture (16%) [46].

Evidence of the successful use of osseointegrated titanium dental implants for the restoration of individual teeth has been reported for anterior teeth more frequently than for posterior teeth. Simon [47] collected data from the charts of patients provided with implant-supported single crowns in posterior quadrants in a prosthodontic practice in southern California. It was reported that 49 patients with 126 implants restored with molar or premolar crowns were recalled for examination after periods ranging from 6 months to 10 years. The implant failure rate was 4.6% with complications of abutment screw loosening (7%) and loss of cement bond (22%) [47].

Even extraoral implants are relied mainly for their fundamental anchoring mechanism to the osteointegration, which intraoral implants depends on heavily, the clinical outcomes and reports appear a slightly different from those on intraoral implants. The quality and quantity of bone available are the most important factors influencing design and placement, and the long-term retention of implants is influenced by implant site, local tissue bed preparation, and hygiene [48]. The successful rehabilitation of patients with craniofacial defects due to trauma, tumor ablation, or congenital deformity depends on the motivation of the patient, careful preoperative planning, interdisciplinary cooperation, and adequate surgical and prosthodontic techniques [48]. Even with these considerations, problems such as

tumor recurrence may require additional surgical resection. [49]. The solution to such recurrence may be autogenous bone grafting or additional implant placement or both, and revision of the prosthesis [49].

Predictable biomechanical retention of nasal prostheses can now be achieved using osseointegrated implants [50]. Flood and Russel [50] treated 14 patients (30 implants), 8 of whom had the implants placed at the time of surgical excision of the tumor. The longest survival so far has been 62 months. Craniofacial osseointegration increases receiving rates of nasal prostheses in patients and improves quality of their lives. In patients, the anatomic sites that have been utilized for implant placement are the nasal bones, the premaxillary area through the nasal fossae, and the anterior wall of the frontal sinus. After a presurgical computerized tomography scan to determine adequacy of bone volume, one conventional threaded hydroxylapatite-coated root-form implant, created for intraoral use was placed in the frontal process of the maxillary bone and two additional conventional implants were placed in the premaxillary area through the nasal fossa. Six months after implant placement, second-stage surgery was completed. A single bar connecting the three implants was fabricated. The removable nasal prosthesis was retained on the bar with two clips. An examination 1 year postsurgery revealed no clinical signs of pathosis. Long-term clinical follow-up of this case should be investigated before use of the frontal process of the maxillary bone for implant [51].

Defects of the external ear could be corrected using prosthetic reconstruction retained by implants [52]. The bar-and-clip design is currently followed for retaining the ear prosthesis. Bars are fixed onto osseointegrated craniofacial implants through a two-stage surgery. Clips embedded in an acrylic housing are used to retain the prosthesis on the bars. The implant is designed as a tapered threaded screw with a ball head abutment that needs only a single-stage surgery. A matching cylindrical metallic socket with silicone snap ring is used for retaining the prosthesis. Two implants can provide adequate retention and stability to the prosthesis. Any loosening could be managed with the replacement of the snap rigs. Socket dimensions are minimal, which are comparable to the natural projection of the ear, thus contributing to good cosmetic appeal of the prosthesis [52]. Gumieiro et al. [53], using bone-anchored titanium implants, treated a patient for auricular rehabilitation. The surgical technique for rehabilitation using implant-retained auricular prostheses seems to be simple. It is associated with low rates of adverse skin reactions and long-term complications. Prostheses anchored by osseointegrated implants seem to provide better retention than do prostheses supported on spectacle frames, less risk of discoloration through the use of adhesives, and better esthetic results than do prostheses anchored in the surgical cavity [53].

Saliva-treated patients are afflicted with head and neck cancer, traumatic injuries to the head and neck, and congenital or developmental defects [54]. These patients benefit from multidisciplinary team management. The head and neck region participates in complex physiologic processes that can often be impeded by these circumstances. Valuation of the patient by the maxillofacial prosthodontist can assist the other members of the team in providing treatment planning options for the patients. Intraoral defects arising from these circumstances can be treated with prosthodontics

that serve to assist with speech, swallowing, and to some degree mastication. If chemotherapeutic or radiation modalities are also used to treat the head and neck, assessment of the patient by the maxillofacial prosthodontist may prove to identify factors that may predispose to undesirable sequelae. Preventive treatment by elective teeth extraction, prosthodontic assessment, and patient education prove to assist in predictable management of these oftentimes complex presenting conditions. Facial defects arising from similar circumstances can be an alternative or adjunct to plastic surgical reconstruction and offer the added advantage of tumor surveillance in susceptible patients [54].

Full oral rehabilitation with a high degree of success is now possible with osteointegrated implants. Osteointegration is a direct connection between living bone and the titanium implant at the level of the light microscope. Osteointegrated implants are currently used to replace single teeth, support fixed bridges, and stabilize full dentures. These implants can also be placed extraorally for attachment of facial prosthesis. The surgical technique used to place implants intraorally into jaws or facial skeletons is performed in two stages using a local anesthetic and/or conscious sedation. During stage I surgery, holes are placed in the jaw using a series of gradually larger diameter burs until the desired diameter and depth of the bony preparation is achieved. The implant is then placed. The implant must remain undisturbed for 4 months for osteointegration to take place. Stage II surgery is then required to remove the mucosa over the implant and place the transmucosal site. After 1–2 weeks of healing, the restorative dentists can take an impression and fabricate the prosthesis. On occasion, it is necessary to augment the height and width of the atrophic jaw with autogenous or allogenic bone grafts prior to implant placement. Bone grafts are sometimes placed on the floor of the nose or the floor of the maxillary sinus. Guided tissue regeneration is a technique used to generate bone within bony defects adjacent to implants. With long-term rates of success (5 years) of 99% for implants placed in the mandible and 95% of those placed in the maxilla, reconstruction of the jaws and cranial facial skeleton with osteointegrated implants has become the treatment of choice [55].

Cervelli et al. [56] reported on their clinical experiences in the reconstruction of complex facial deformities using titanium osteointegrated implants for the retention of soft silicone prostheses. They also evaluated the importance of this surgical technique as a viable alternative to traditional reconstructive procedures using autologous grafts both in patients with severe osteomuscular defects and corrective surgery of unsuccessful reconstruction operations. The patients who underwent implantation operation were studied by CT 3D and Single Photon Emission Computerized Tomography (SPECT) procedures to evaluate osseointegration at 3 weeks, and at 3, 6, 12, and 24 months. The study demonstrates that the radiation emission peaks 3 weeks after surgery with the maximum remodeling activity and after the functional loading of the implants 3 months after surgery. High uptake past the eighth month after surgery has never been detected and must be considered abnormal. SPECT offers the possibility of obtaining a three-dimensional reconstruction of the photon emission of selected structures. The use of nuclear medicine methods in addition to traditional-type radiological procedures introduces new

possibilities, although still in the clinical experimentation phase, for the long-term follow-up of inserted implants in craniofacial rehabilitation.

Facial prosthetics can be a life-changing milestone for patients who have lost an eye, ear, or nose or sustained damage to intraoral structures. For many years, such people were forgotten patients who had to live with these obvious deformities. Many of them avoided social situations and interactions. But thanks to advances in science and technology, a near-normal appearance can be restored with a new prosthetic eye, ear, or nose. Trauma (car accidents, burns, occupational accidents), head and neck cancer, and congenital defects are the most common reasons for full or partial loss of eye, ear, nose, jaw bone, or other head and neck structures. Patients faced with these defects may be able to choose between surgical and prosthetic reconstructions, depending on the location and size of the defect. Sometimes the decision is between a prosthesis and nothing at all, for people who live in rural areas and/or lack insurance coverage. But even if people have geographical access to a center of excellence and the financial means to avail themselves of the best possible care, they may choose to live with a deformity rather than to have the hassle of cleaning and replacing a prosthetic device on a daily basis [57].

The use of craniofacial implants is an effective treatment for patients with deformities, burns, and cancer sequelae [58,59]. The sites with the most successful implants are the auricular, nasal, and orbital regions. Furthermore, other factors can affect the implant longevity such as irradiated area, surgical technique, bone quality and quantity, macrostructure, and microstructure of the implant, maintenance, and systemic factors [58].

8.4 Surface and Interface Characterizations

Defining the nature of biomaterial surfaces is crucial for understanding interactions with biological systems. Surface analysis requires special techniques and instruments considering the analysis of a 50 Å-thick region in a 1 mm² area on the surface of a specimen that is 1 mm in total thickness. Devices intended to be implanted or interfaced intimately with living tissue may be composed of a variety of materials. Understanding the biological performance and efficacy of these biomaterials requires a thorough knowledge of the nature of their surfaces. The nature of the surface can be described in terms of surface chemistry, surface energy, and morphology [60].¹

Biomaterials and implant research is a challenging, complex, and extremely cross-disciplinary field. It involves clinical surgery and essentially all other areas of medical science, as well as biology, chemistry, physics, and the technical sciences. Claims for osteointegration, fibroosteal integration, bone bonding, and

¹ Suppose we have a cube with 1 cm on each face. The ratio of molecules involved in the bulk (interior) to that of surface can be estimated as follows. Let the size of molecule be a^3 (in cm³). The ratio = number of bulk molecules/number of surface molecules = $(1/a^3)/\{6 \times (1/a)^2\} = 1/6a$. If $a = 5 \times 10^{-8}$ cm or 50 nm, the ratio = $1/(6 \times 5 \times 10^{-8}) = 1/(3 \times 10^{-7})$, indicating that surface microanalysis needs at least 3×10^7 times higher sensitivity than the bulk analysis requires.

bony ankylosis abound, but there is little precise knowledge of the actual interface between implant and tissue, and of the factors that influence host response and the long-term integrity of the implant system. It is well known that the surface chemistry, surface energy, and surface topography govern the biological response to an implanted material. The tissue response to a dental (or surgical) implant may involve physical factors such as size, shape, surface texture, and relative interfacial movement, as well as chemical factors associated with the composition and surface structure [61–63].

Ti material is one of the most commonly used biomaterials for dental and orthopedic applications. Its excellent tissue compatibility is mainly due to the properties of the stable oxide layer which is present on the surface. Lausmaa and Kasemo [64] characterized the surface composition of unalloyed Ti implant materials, prepared according to procedures commonly used in clinical practice (machining, ultrasonic cleaning, and sterilization). The surface of the implants is found to consist of a thin surface oxide which is covered by a carbon-dominated contamination layer. The thickness of the surface oxides is 2–6 nm, depending on the method of sterilization. The surface contamination layer is found to vary considerably from sample to sample and consists of mainly hydrocarbons with trace amounts of calcium, nitrogen, sulfur, phosphorous, and chlorine. Some differences in surface composition between directly prepared surfaces and some possible contamination sources are identified [64].

According to Sutherland et al. [65], there are three major reasons for the apparent success of Ti implants. First, Ti, although a highly reactive metal, forms a dense, coherent passive oxide film, preventing the ingress of corrosion products into the surrounding tissue. Second, bone is in a dynamic state, continually resorbing old bone and laying down new. One implant variable in the rate of bone remodeling is the difference in elastic moduli between bone and its replacement. Normally the larger this difference, the more rapidly bone changes take place. Ti is particularly good in this regard because of its lower elastic moduli. The third factor tending to promote osteointegration is the biochemical properties of the oxide coating. The surface is also known to have at least two types of hydroxyl groups attached to it. TiO_2 is nonconducting, but electrons can tunnel through the layer. Thin oxide layers can allow the passage of electrons, leading to conformational changes and denaturing of proteins. Medical grade Ti samples were examined using XPS before and after immersion in various proteins. Additionally, an implant removed from a patient following clinical failure was examined using scanning ion and electron microscopy. The surface of the as-received samples was found to be mainly TiO_2 , with contamination of $\text{H}_2\text{O}/\text{OH}^-$, Ca, and N, which remained after autoclaving. The immersed proteins adhered to the Ti surface, possibly via a Ca–O link. The failed clinical sample was found to be partially fibrously encapsulated with evidence of calcification. Small amounts of $\text{TiO} \cdot \text{OH}$ were detected at the fibrous periphery [65], supporting the theory of Tengvall and Lundstrom [66] that *in vivo* Ti implants are covered in a gel of this material.

The chemical state of the surfaces of three types of osteointegrated Ti implants was analyzed by Sawase et al. [67]. It was reported that moderately rough surfaces

show stronger bone responses than smoother or rougher surfaces. This is supported by a review done by Albrektsson et al. [68,69], indicating that the majority of currently marketed implants are moderately rough. Oral implants permit bone ingrowth into minor surface irregularities—biomechanical bonding or osteointegration. Four- and seven-year implanted blade-type shape memory effect (SME) NiTi dental implants were microanalyzed to characterize the surfaces by Oshida [70]. It was found that the entire surfaces of SME NiTi implants were covered with many bubbles and craters which were also found by James [71]. These surface irregularities have averaged sizes of 2–10 μm in diameter. Furthermore, the 3D finite element analysis method (FEM) stress analysis showed that several characteristic portions—for example, the tip of the head, neck, and bending portions of the implant—where more bubbles and craters were formed than on the other portions of the blades [70], were subject to the highest von Mises stress levels [72]. Hence, it is suggested that stress-assisted dissolution of nickel would take place at the interface between the NiTi implant and the living hard tissue [70].

Fox and Miller [73] characterized the *in vitro* and *in vivo* electrochemical behavior of CpTi using a specialized osseous implant in conjunction with the electrochemical impedance spectroscopy (EIS) measurement technique. Studies performed *in vitro* were used to verify the operation of transducer and develop methods of deconvoluting EIS data. This method was subsequently used to describe an electrochemical equivalent circuit model of the surface oxide and electrical double-layer capacitance of CpTi in the endogenous electrolyte found in the medullary compartment of a baboon tibia. Kinetic profiles of the double-layer capacitance and the polarization resistance were constructed from multiple *in vitro* and *in vivo* EIS measurements performed over 60 min at 0 V (vs. Ag/AgCl) conditioning potential. The profiles demonstrated that the growth of surface oxides was biphasic, with rapid decrease in the double-layer capacitance occurring within 20 min and reaching steady-state conditions at approximately 40 min. These data suggested that a passive, stable biofilm formed on the CpTi surface *in vivo* and *in vitro* [73]. There is another study using EIS technique. Surfaces of CpTi and Ti–6Al–4V were subjected to simultaneous polarization/impedance testing and *in situ* electrochemical atomic force microscopy (AFM) imaging to evaluate how the structure and properties of the passive oxide film is affected by varying potential and hydration. Simultaneous (AFM) imaging of dry surfaces, initially hydrated surfaces, and surfaces immersed and changing with potential revealed that all sample surfaces were covered with protective Ti oxide domes that grew in area and coalesced due to hydration and as a function of increasing applied voltage and time [74].

In order to enhance the tissue-adhering strength of titanium implants, various physical and chemical treatments have been proposed and conducted. However, the majority of evaluations on such bonding strengths are normally found in bone-bonding strength, tissue-bonding strength, or interfacial observation on the order of several millimeters to microns depth. Interaction between biomaterials and living tissue is strongly influenced by the surface characteristics and surface adsorption of protein or extracellular matrices in the near-surface area, which is more important. Such interaction areas are on the order of nm scale. In order to reach this level of

microanalysis, the surface plasmon resonance (SPR) method has been proposed to analyze the real-time interaction between titanium surfaces and biomolecules. The surface plasmon wave is a dense wave of electrons existing on a metallic surface. Hirata [75] developed a unique SPR sensor accompanied by titanium that was oxidized in air. It was reported that (i) although the titanium dioxide SPR sensor is effective in optics and industrial fields, since the biofunctionality and bioactivity of biomolecules on preoxidized metallic titanium as artificial bone or dental implant are more important, a metallic titanium SPR sensor is more effective and (ii) this SPR sensor is more useful to investigate the biocompatibility in nanometer regions.

Ti–6Al–7Nb in its standard implant form has been previously shown to be detrimental to fibroblast growth and colonization on its surface. Specific aspects of the Ti–6Al–7Nb topography have been implicated; however, the contribution of its unique surface chemistry to the cell behavior was unknown. By evaporating either gold or titanium on the surface of standard Ti–6Al–7Nb, two different model surface chemistries could be studied with the same characteristic standard Ti–6Al–7Nb topography. CpTi and stainless steel were also treated in a similar manner. All materials elicited behavior similar to their uncoated counterparts. For coated stainless steel and CpTi, the cell proliferation was observed; cells were well spread and displayed mature focal adhesion sites and associated cytoskeletal components. For Ti-coated alloy, cell proliferation was compromised, cells remained rounded, filopodia attached and seemed to probe the surface, especially the beta-phase particles, and both the focal adhesion sites and the microtubule network were disrupted by the presence of these particles. These results confirmed that in the instance of Ti alloy, the topography was the primary cause for the observed stunted cell growth. For biomaterials studies, the standardization of surface chemistry used here is a valuable tool in allowing vastly different materials and surface finishes to be compared solely on the basis of their topography [76].

Mechanical compatibility between a coating and a substrate is important for the longevity of implant materials. While previous studies have utilized the entire coating for analysis of mechanical compatibility of the surface, this study focuses on the nanoindentation of a uniformly and thermally sprayed splat. Hydroxyapatite was thermally sprayed to create a homogeneous deposit density, as confirmed by micro-Raman spectroscopy of amorphous calcium phosphate. Substrates were CpTi, Ti–6Al–4V, Co–Cr alloy, and stainless steel. Nanoindentation revealed that splats deposited on different metals have similar hardness (4.2 GPa) and elastic modulus (80 GPa) values. The mechanical properties were affected by the substrate type more than residual stresses, which were found to be low. It is recommended that amorphous calcium phosphate be annealed to relieve the quenching stress, or that appropriate temperature histories are chosen to relax the stress created in cooling the coating assembly [77]. Due to oxidation and adsorption of chloride and hydroxyl anions, the surface of titanium implants is negatively charged. A possible mechanism of the attractive interaction between the negatively charged Ti surface and the negatively charged osteoblasts is described theoretically. It is shown that adhesion of positively charged proteins with internal charge distribution may give rise to attractive interaction between the Ti surface and the osteoblast membrane.

A dynamic model of the osteoblast attachment is presented in order to study the impact of geometrically structured Ti surfaces on the osteoblasts attachment. It is indicated that membrane-bound protein complexes may increase the membrane protrusion growth between the osteoblast and the grooves on titanium surface and thereby facilitates the adhesion of osteoblasts to the Ti surface. On the other hand, strong local adhesion due to electrostatic forces may locally trap the osteoblast membrane and hinder the further spreading of osteointegration boundary. We suggest that the synergy between these two processes is responsible for successful osteointegration along the titanium surface implant [78].

The bone response to CpTi (grade I) and Ti–6Al–4V alloy after 8 weeks in rabbit tibia was evaluated [79]. Interface microscopy and SEM were used for surface analyses. Transmission electron microscopy was used for investigation of surface crystallinity and chemistry after preparation of ultrathin sections using focused ion beam microscopy. Three different embedding resins commonly used for histological preparation were evaluated with respect to adaptation to a turned implant surface. The histological evaluation revealed osteointegration for both Ti materials, but no quantitative differences in bone contact and bone area were detected. Because a separation of implant and tissue occurred in the interface between implant and bone embedded in acrylic resin, additional factors related to implant surface properties technical procedures are likely to influence the possibilities to prepare ultrathin sections [79].

Infection of an orthopedic prosthesis is undesirable and causes a decrease in the success rate of an implant. Reducing the adhesion of a broad range of bacteria could be an attractive means to decrease infection and allow for subsequent tissue integration with the biomaterial surface. In the *in vitro* study, nanometer-sized topographical features of Ti surface, which have been previously shown to enhance select protein adsorption and subsequent osteoblast (bone-forming cell) functions, were investigated as a means to reduce bacteria adhesion also. The study examined the adhesion of *Staphylococcus aureus*, *S. epidermidis*, and *Pseudomonas aeruginosa* on conventional Ti, nanorough Ti produced by electron beam evaporation, and nanotubular and nanotextured Ti produced by two different anodization processes. This study found that compared to conventional (nanosmooth) Ti, nanorough Ti surfaces produced by electron beam evaporation decreased the adhesion of all of the aforementioned bacteria the most. The conventional and nanorough Ti surfaces were found to have crystalline TiO₂, while the nanotubular and nanotextured Ti surfaces were found to be amorphous. The surface chemistries were similar for the conventional and nanorough Ti, while the anodized Ti surfaces contained fluoride. Therefore, the results of this *in vitro* study demonstrated that certain nanometer-sized Ti topographies may be useful for reducing bacteria adhesion while promoting bone tissue formation and, thus, should be further studied for improving the efficacy of Ti-based orthopedic implants [80]. Push-out tests can be used to estimate the shear strength of the bone–implant interface. Although numerous such experimental studies have been published in the literature, it appears to be needed for further development of accurate models to simulate implant stability. A specific experimental push-out study employed two different bone–implant interface

models. The implant was a porous-coated Ti–6Al–4V retrieved 4 weeks postoperatively from a dog model. The purpose was to find out which of the interface models could replicate the experimental results using physical meaningful input parameters. The results showed that a model based on partial bone ingrowth (ingrowth stability) is superior to an interface model based on friction and prestressing due to *après fit* (initial stability). Even though the study was limited to a single experimental setup, the authors suggest that the presented methodology can be used to investigate implant stability from other experimental push-out model. This would eventually enhance the much-needed understanding of the mechanical response of the bone–implant interface and help to quantify how implant stability evolves with time [81]. Osteointegration of porous materials for implants made for Co–Cr–Mo and titanium with Bioglass type-S2 was studied [82]. All the materials were prepared using cold pressing and sintering. The research was made on castrated goats averaging 1 year of age. Bone growth process on surfaces of implants made with additional bioglass was found significantly intense. The amount of osseous tissue and the number of connection points significantly increased. On surfaces of titanium implants, few areas of stochastic callus formation were observed. In that case, areas of preferential bone integration have uneven surface due to technological process. A significant difference appears in osseous tissue growth morphology on implant surface. In porous implants, bone grows around the pores of an implant. The obtained results showed that (i) porosity influences callus growth intensity beneficially on the implant structure and (ii) use of bioglass increases bone growth intensity on implant surface [82].

Measurement of the stress and strain applied to implants and bone tissue in the human body are important for fracture prediction and evaluations of implant adaptation. Fujisaki et al. [83] suggested that the strain of Ti materials can be measured by X-ray diffraction (XRD) techniques when applying XRD to the skin tissue-covered Ti. Strain measurements were conducted under bending loads applied to the Ti specimen. It was reported that (i) the effect on skin tissue was absorption of X-rays as well as the X-rays scattered from the physiological saline contained in the tissue, (ii) the X-rays scattered by the physiological saline creates a specific background pattern near the peaks from (002) and (011) lattice planes of Ti in the XRD profile, and (iii) diffracted X-rays from Ti were detected after being transmitted through 1-mm-thick skin tissue by characteristic X-ray of Mo K α .

8.5 Reactions in Chemical and Mechanical Environments

Biocompatibility of metallic materials essentially equates to corrosion resistance because it is thought that alloying elements can only enter the surrounding organic system and develop toxic effects by conversion to ions through chemical or electrochemical process. There are a number of alloys whose tolerance in implanted forms can be as good or as adequate as the ceramic and polymeric materials used in biomedical applications. After implant placement, initial healing of the bony compartment is characterized by the formation of blood clots at the wound site, protein

adsorption, and adherence of polymorphonuclear leukocytes. Then, approximately 2 days after placement of the implant, fibroblasts proliferate into the blood clot, organization begins, and an extracellular matrix is produced. Approximately 1 week after the implant is placed, appearance of osteoblast-like cells and new bone is seen. New bone reaches the implant surface by osteoconduction (through growth of bone over the surface and migration of bone cells over the implant surfaces) [84].

In the cells of living organisms, a delicate equilibrium exists between the quantities of some metals needed in catalytic processes and the level at which these same metals become toxic. Some other metals have no part in the biological cycle but might be present in implants used in surgery. Chemical interaction between implants and tissue requires exchange of ions between the solid metal and the biological structure, e.g., by complex formation with proteins. There should be at least three factors: (1) Corrosion frees metal ions, and an immediate conclusion is that slow dissolution of the metal, even if it contains highly toxic elements, produces a weak interaction. (2) The ions can enter the body chemistry or react with water to form surface hydroxides or oxides. If stable hydroxides or oxides are formed, the dissolved metal concentration will be small and again a possible interaction with the biological structure will be less likely. But solubility of these inorganic compounds can be altered in tissue fluids, and the complex formation of such compounds might even redissolve. (3) A third factor which determined a local metal concentration is related to transport, essentially by chemical diffusion. Ions and any dissolved electrolyte components created at the corroding metal surface move away in a concentration gradient, and if diffusion is slow, the local concentration of such electrolyte components will become high. It should also be mentioned that this diffusion, together with an element's solubility, is necessary for systemic effects [85]. Corrosion is one of the major processes that cause problems when metals are used as implants in the body. Their proper application to minimize such problems requires that one have an understanding of principles underlying the important degradative process of corrosion. To have such an understanding will result in proper application, better design, choice of appropriate test methods to develop better designs, and the possibility of determining the origin of failures encountered in practice [85,86].

All oral and maxillofacial implants are meant to support forces *in vivo*, so it is obvious that biomechanics plays a major role in implant design. Cook [87] and Brunski [88] pointed out the following biomechanical issues as the most important: (1) what are the *in vivo* loadings that dental implants must be designed to resist, (2) what factors are most important in controlling how the *in vivo* loads are transmitted to interfacial tissues, what are the stress and strain states in bone around the implant, and how can they be controlled, (3) what are safe versus dangerous levels of stress and strain in interfacial bone, and (4) what biomechanical factors contribute most to implants success or failure. It was reported that the potential for long-term implant fixation and the ability to treat younger, more active patients are part of the appeal of porous-coated implants. However, because porous implants eliminate poly(methylmethacrylate) bone cement, initial fixation of the implant is no longer guaranteed, and this may compromise the initial success and long-term stability of the device.

Biomechanics involved in implantology should include at least (1) the nature of the biting forces on the implants, (2) transferring of the biting forces to the interfacial tissues, and (3) the interfacial tissues reaction, biologically, to stress transfer conditions. Interfacial stress transfer and interfacial biology represent more difficult, interrelated problems. Hence, many engineering variables such as implant shape, elastic modulus, and extent of bonding between implant and bone can affect the stress transfer conditions. The successful clinical results achieved with osteointegrated dental implants underscore the fact that such implants easily withstand considerable masticatory loads. In fact, one study showed that bite forces in patients with these implants were comparable to those in patients with natural dentitions. A critical aspect affecting the success or failure of an implant is the manner in which mechanical stresses are transferred from the implant to bone. It is essential that neither implant nor bone be stressed beyond the long-term fatigue capacity. It is also necessary to avoid any relative motion that can produce abrasion of the bone or progressive loosening of the implants. An osteointegrated implant provides a direct and relatively rigid connection of the implant to the bone. This is an advantage because it provides a durable interface without any substantial change in form or duration. There is a mismatch of the mechanical properties and mechanical impedance at the interface of Ti and bone that would be evident at ultrasonic frequencies. It is interesting to observe that from a mechanical standpoint, the shock-absorbing action would be the same if the soft layer were between the metal implant and the bone. In the natural tooth, the periodontium, which forms a shock-absorbing layer, is in a position between the tooth and jaw bone [89]. Natural teeth and implants have different force transmission characteristics than bone. Compressive strains were induced around natural teeth and implants as a result of static axial loading, whereas combinations of compressive and tensile strains were observed during lateral dynamic loading. Strains around the natural tooth were significantly lower than the opposing implant and occluding implants in the contralateral side for most regions under all loading conditions. There was a general tendency for increased strains around the implant opposing natural tooth under higher loads and particularly under lateral dynamic loads [90].

The above statement is further understood if a natural dentition and implant system are compared, as seen in [Figure 8.1](#). It can be pointed out that the most distinct difference between these two is the fact that the natural dentition has a periodontal membrane, functioning as a mechanical shock absorber, as well as a solid bonding between tooth root surface and surrounding tissue, whilst with the implant, there are osteointegration and functional ankylosis. From a biomechanistic viewpoint, with natural teeth, there are shock absorption mechanisms and stress distribution; on the other hand, with implants, the stress tends to be concentrated and increases in crestal bone. It is true that blood supply in natural teeth is much higher than that with implant systems.

The interface mechanical characteristics and histology of CpTi and HA-coated CpTi were studied by Cook et al. [91]. It was reported that (i) histologic evaluation in all cases revealed mineralization of interface bone directly onto the HA-coated implant surface, becoming part of the implant composite system and (ii) the

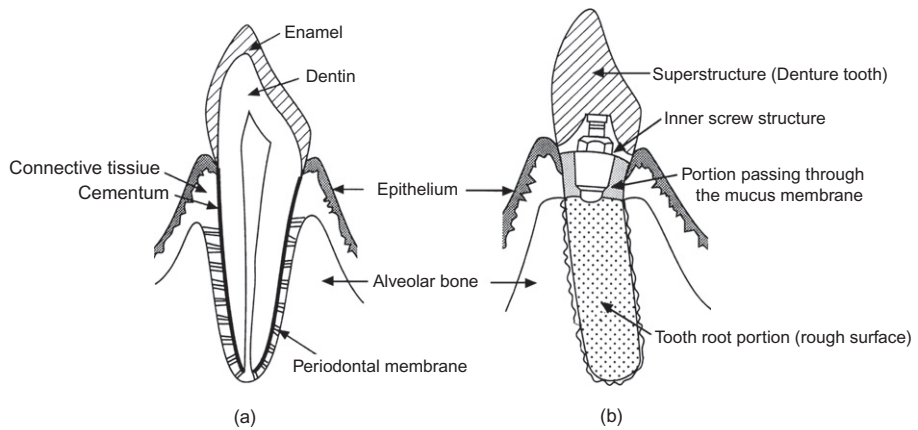


Figure 8.1 Schematic comparison between (A) a natural tooth and (B) an implant tooth.

uncoated implants had a thin fibrous interpositional layer present in most areas, with projections of bone in apposition to the implant surface in a limited number of locations, indicating that the HA-coated Ti system may be attractive for use in endosseous dental implant applications [91]. Masticatory forces acting on dental implants can result in undesirable stress in adjacent bone, which in turn can cause defects and the eventual failure of implants. It was reported that (i) the maximum stress areas were located around the implant neck, (ii) the decrease in stress was the greatest (31.5%) for implants with a diameter ranging from 3.6 to 4.2 mm, and (iii) an increase in the implant length also led to a decrease in the maximum von Mises equivalent stress values; the influence of implant length, however, was not as pronounced as that of implant diameter. It was further mentioned that an increase in the implant diameter decreased the maximum von Mises equivalent stress around the implant neck more than an increase in the implant length, as a result of a more favorable distribution of the simulated masticatory forces applied [92]. At present, load-bearing implants are designed on a deterministic basis in which the structural strength and applied loading are given fixed values, and global safety factors are applied to cover any uncertainties in these quantities and to design against failure of the component [93]. This approach will become increasingly inappropriate as younger and more active patients demand more exactness, and as devices become more complex. Browne et al. [93] described a preliminary investigation in which a scientific and probabilistic technique is applied to assess the structural integrity of the knee tibial tray. It was envisaged that by applying such a technique to other load-bearing biomedical devices, reliability theory may aid in future lifting procedures and materials/design optimization.

Although one of the most common procedures performed in implant dentistry is a single-tooth replacement, some cases offer two implants for three crowns—a three-unit implant. The influence of implant number and cantilever design on stress distribution on bone has not been sufficiently assessed for the mandibular

overdenture. Sadowky and Caputo [94] reported that while all four prostheses demonstrated low stress transfer to the implant, the plunger-retained prosthesis caused more uniform stress distribution to the ipsilateral terminal abutment compared to the slip-retained prosthesis, and provided retention security under tested loads. The plunger-retained prosthesis retained by two implants provided better load sharing from the ipsilateral edentulous ridge than the clip-retained prosthesis retained by three implants, and lower resultant stresses were seen on the implants [94].

By means of FEM, stress distribution in bone around implants was calculated with and without a stress-absorbing element [95]. A freestanding implant (i.e., single unit) and an implant connected with a natural tooth were simulated. It was reported that (i) for the freestanding implant, the variation in the MOE of the stress-absorbing element had no effect on the stresses in bone; changing the shape of the stress-absorbing element had little effect on the stresses in cortical bone and (ii) for the implant connected with a natural tooth, a more uniform stress was obtained around the implant with a low MOE of the stress-absorbing element. It was also found that the bone surrounding the natural tooth showed a decrease in the height of the peak stresses [95]. Mechanical *in vitro* tests of the Brånemark implant indicated that the screw joint which attaches the prosthetic gold cylinder and the transmucosal abutment to the fixture forms a flexible system. Calculations of vertical load distribution based on measured flexibility data demonstrated that the forces are shared almost equally between the tooth and the implant, even without taking the flexibility of the surrounding bone or the prosthesis into account. The therapy of a single Brånemark implant connected to a natural tooth should be considered without any additional element of a flexible nature. Mechanical tests and theoretical considerations, however, indicate that the transverse mobility of the connected tooth should be limited and that the attachment of the prosthesis to the tooth should be a rigid design to avoid gold screw loosening [96]. The stress distribution pattern clearly demonstrated a transfer of preload force from the screw to the implant during tightening. A preload of 75% of the yield strength of the abutment screw was not established using the recommended tightening torques. Using FEM, a torque of 32 N cm applied to the abutment screws in the implant assemblies was studied in the presence of a coefficient of friction of 0.26 and resulted in a lower than optimum preload for the abutment screws. It was then mentioned that in order to reach the desired preload of 75% of the yield strength, using the 32 N cm torque applied to the abutment screws in the implant assemblies studied, the coefficient of friction between the implant components should be 0.12 [97].

The fractured surface of a retrieved Ti screw and metallurgical structures of a dental implant system were analyzed by Yokoyama et al. [98]. The outer surface of the retrieved screw had a structure different from that of the as-received screw. It was confirmed that a shear crack initiated at the root of the thread and propagated into the inner section of the screw. Gas chromatography revealed that the retrieved screw had absorbed a higher amount of hydrogen than the as-received sample, suggesting that the fracture is, to some extent, related to the hydrogen embrittlement. The grain structure of a Ti screw immersed in a solution known to induce hydrogen absorption showed features similar to those of the retrieved screw. It was concluded

that Ti in a biological environment absorbs hydrogen and this may be the reason for delayed fracture of a Ti implant [98]. It is known that the high-cycle fatigue strength of porous-coated Ti-6Al-4V is approximately 75% less than the fatigue strength of uncoated Ti-6Al-4V [99]. It was mentioned that (i) the fatigue strength of smooth-surfaced Ti-6Al-4V subjected to hydrogen treatments is 643–669 MPa, significantly greater than that of beta-annealed Ti-6Al-4V (497 MPa) and also greater than that of preannealed, equiaxed Ti-6Al-4V (590 MPa) and (ii) the fatigue strength of porous-coated Ti-6Al-4V, however, is independent of microstructure, suggesting that the notch effect of the surface porosity does not allow the material to take advantage of the superior fatigue crack initiation resistance of refined alpha-grain size [97]. Bone tissue ingrowth into porous-metal-coated implants is often the preferred method of prosthetic fixation in younger and more active patients [87,88]. The short-term clinical results of porous-coated implants have been good. The long-term success of any implants is determined, in part, by the ability of the material to withstand repetitive loading. Kohan et al. [100] utilized acoustic emission (AE) events and event intensities (e.g., event amplitude, counts, duration, and energy counts) to analyze the fatigue process of uncoated and porous-coated Ti-6Al-4V. AE provides the ability to spatially and temporally locate multiple fatigue cracks in real time. Fatigue of porous-coated Ti-6Al-4V is governed by a sequential, multimode fracture process of: transverse fracture in the porous coating; sphere/sphere and sphere/substrate debonding; substrate fatigue crack initiation; and slow and rapid substrate fatigue crack propagation. Because of the porosity of the coating, the different stages of fracture within the coating occur in a discontinuous manner. Changes in the AE event rate also correspond to changes in crack extension rate and may therefore be used to predict failure. It was reported that (i) intergranular fracture and microvoid coalescence generated the highest AE event amplitudes (100 dB), whereas plastic flow and friction generated the lowest AE event amplitudes (55–65 dB) and (ii) fractures in the porous coating were characterized by AE event amplitudes of less than 80 dB [100].

A satisfactory clinical outcome in dental implant treatment relies on primary stability for immediate load bearing. While the geometric design of an implant contributes to mechanical stability, the nature of the implant surface itself is also critically important. Biomechanical and microcomputerized tomographic evaluation of implant osteointegration was performed to compare alternative structural, chemical and biochemical, and/or pharmaceutical surface treatments applied to an identical established implant design. Dental implants with the same geometry but with six different surface treatments were tested *in vivo* in a sheep model. Periimplant bone density and removal torque were compared at 2, 4, and 8 weeks after implantation. Implant surfaces tested were: sand-blasted and acid-etched titanium (Ti), sand-blasted and -etched zirconia (ZrO_2), Ti coated with calcium phosphate (CaP), Ti modified via anodic plasma-chemical treatment (APC), bisphosphonate-coated Ti (Ti + Bisphos), and Ti coated with collagen containing chondroitin sulfate (CS). All dental implants were well integrated at the time of sacrifice. There were no significant differences observed in periimplant bone density between implant groups. After 8 weeks of healing, removal torque values for Ti, Ti + CaP, Ti + Bisphos,

and Ti + collagen + CS were significantly higher than those for zirconia and Ti + APC. Though the sand-blasted/acid-etched Ti implant can still be considered, the reference standard surface for dental implant, functional surface modifications such as a bisphosphonate or collagen coating seem to enhance early periimplant bone formation and should be studied further [101]. Mechanical loading factors at the bone–implant interface are critical for the osteointegration and clinical success of the implant treatment. The aim of the study was to study the effects of mechanical strain on the orthopedic biomaterial Ti–6Al–4V/osteoblast interface, using an *in vitro* model. Homogeneous strain was applied to human bone marrow-derived osteoblasts cultured on Ti–6Al–4V, at physiological levels (strain magnitudes 500 microstrain and 1000 microstrain, at frequencies of load application 0.5 and 1 Hz), by a mechano-stimulatory system, based on the principle of four-point bending. Semi-quantitative reverse transcription-polymerase chain reaction was used to determine the mRNA expression of Cbfa1 and osteocalcin at different loading conditions. Mechanical loading was found to contribute to the regulation of osteoblast differentiation by influencing the level of the osteoblast-specific transcription factor Cbfa1, both the mRNA and protein level, and also the level of osteocalcin, which is regarded as the most osteoblast-specific gene. Both genes were differentially expressed shortly after the application of different mechanical stimuli, terms of strain frequency, magnitude, and time interval. Media conditioned from mechanically stressed human bone marrow-derived osteoblasts stimulated DNA synthesis more intensely compared to media conditioned from unstressed control cultures, indicating that mechanical strain induces the release of a mitogenic potential that regulates cell proliferation [102]. The term “stress shielding” can be defined as the reduction in bone density (osteopenia) as a result of removal of normal stress from the bone by an implant (e.g., the femoral component of a hip prosthesis). This is because by Wolff’s law, bone in a healthy person or animal will remodel in response to the loads it is placed under. Therefore, if the loading on a bone decreases, the bone will become less dense and weaker because there is no stimulus for continued remodeling that is required to maintain bone mass [103–105].

8.6 Reaction in Biological Environment

A goal of biomaterials research has been, and continues to be, the development of implant materials which are predictable, controlled, guided, with rapid healing of the interfacial hard and soft tissues. The performance of biomaterials can be classified in terms of the response of the host to the implant and the behavior of the material in the host. This is actually related to which side we are looking at the host (vital tissue)/foreign materials (implant) interface. The event that occurs almost immediately upon implantation of metals, as with other biomaterials, is adsorption of proteins. These proteins come first from blood and tissue fluids at the wound site and later from cellular activity in the interfacial region. Once on the surface, proteins can desorb (undenatured or denatured, intact, or fragment),

remain, or mediate tissue–implant interaction [106]. The host response to implants placed in bone involves a series of cell and matrix events, ideally culminating in tissue healing that is as normal as possible and that ultimately leads to intimate apposition of bone to the biomaterials, namely the definition of osteointegration. For this intimate contact to occur, gaps that initially exist between the bone and implant at surgery must be filled initially by a blood clot, and the bone damaged during preparation of the implant site must be repaired. During this time, unfavorable conditions, for example, micromotion (a biomechanical factor) will disrupt the newly forming tissue, leading to the formation of a fibrous capsule [107]. The criteria for clinical success of osteointegration are based on functionality and compatibility, which depend on the control of several factors including: (1) biocompatible implant material using commercially pure titanium, (2) design of the fixture (a threaded design is advocated creating a larger surface per unit volume as well as even distribution loading forces), (3) the provision of optimal prosthodontic design and implant maintenance to achieve ongoing osteointegration, (4) specific aseptic surgical techniques and a subsequent healing protocol which are reconcilable with the principles of bone physiology, which would incorporate a low-heat/low-trauma regimen, a precise fit and the two-stage surgery program, (5) a favorable status of the host–implant site from a health and morphologic standpoint, (6) nonloading of the implant during healing as a basic tenet of osteointegration, and (7) the defined macro-microscopic surface of the implant as it relates to the host tissue [107]. The implantation of any foreign material in soft tissue initiates an inflammatory response. The cellular intensity and duration of the response is controlled by a variety of mediators and determined by the size and nature of the implanted material, site of implantation, and reactive capacity of the host [108].

Dental implants vary markedly in the topography of the surfaces that contact cells. According to Brunette [109], there are four principles of cell behavior observed in cell culture to explain to some extent the interactions of cells and implants. (1) Contact guidance aligns cells and collagen fibers with fine grooves (known as machine toolmarks). (2) Rugophilia describes the tendency of macrophages to prefer rough surfaces. (3) The two-center effect can explain the orientation of soft connective tissue cells and fibers attached to porous surfaces. (4) Haptotaxis may be involved in the formation of capsules around implants with low-energy surfaces [109]. Surface roughness has been shown to be an influencing parameter for cell response. Bigerle et al. [110] compared the effect of roughness organization of Ti–6Al–4V or CpTi on human osteoblast response (proliferation and adhesion). Surface roughness is extensively analyzed at scales above the cell size (macroroughness) or below the cell size (microroughness) by calculation of relevant classic amplitude parameters and original frequency parameters. It was found that (i) the human osteoblast response on electroerosion Ti–6Al–4V surfaces or CpTi surface was largely increased when compared to polished or machine-tooled surfaces after 21 days of culture and (ii) the polygonal morphology of human osteoblast on these electroerosion surfaces was very close to the aspects of human osteoblast *in vivo* on human bone trabeculae. Based on these findings, it was concluded that electroerosion technique for creating a rough surface is a

promising method for the preparation of bone–implant surfaces, as it could be applied to the preparation of most biomaterials with complex geometries [110].

Ti oxide films were synthesized on Ti, Co alloy, and low-temperature isotropic pyrolytic carbon by the ion beam enhanced deposition technique [111], by which the amorphous nonstoichiometrical Ti oxide films (TiO_{2-x}) were obtained. Blood compatibility of the films was evaluated by clotting time measurement, platelet adhesion investigation, and hemoptysis analysis. It was found that (i) the blood compatibility of the material was improved by the coating of Ti oxide films, (ii) the nonstoichiometric TiO_{2-x} has n-type semiconductive properties because very few cavities exist in the valence band of TiO_{2-x} (charge transfer is difficult from the valence band of fibrinogen into the material), and (iii) on the other hand, the n-type semiconductive TiO_{2-x} with a higher Fermi level can decrease the work function of the film, which makes electrons move out from the film easily. As a result, it was concluded that the deposition of fibrinogen can be inhibited and blood compatibility improved [111].

Favorable wound healing responses around metallic implants depend on critical control of the surgical and restorative approaches used in dental implant treatments. One critical parameter that has not been biologically studied is the role of a clean, sterile oxide surface on an implant. This oxide surface can alter the cellular healing responses, and potentially the bone remodeling process, depending on the history of how that surface was milled, cleaned, and sterilized prior to placement. Based on this background, Stanford et al. [112] evaluated the phenotypic responses of rat calvarial osteoblast-like cells on CpTi surfaces. These surfaces were prepared to three different clinically relevant surface preparations (1 μm , 600 grit, and 50 μm grit sand blasting), followed by sterilization with either ultraviolet light, ethylene oxide, argon plasma cleaning, or routine clinical autoclaving. It was found that (i) osteocalcin and alkaline phosphatase, but not collagen expression, were significantly affected by surface roughness when these surfaces were altered by argon plasma cleaning and (ii) on a per-cell basis, levels of the bone-specific protein, osteocalcin, and enzymatic activity of alkaline phosphatase were highest on the smooth 1 μm polished surface and lowest on the roughest surface for the plasma-cleaned CpTi [112].

Carlsson et al. [113] investigated the glow-discharged Ti implants with a presumed high surface energy and conventionally prepared and sterilized CpTi implants which were inserted in the rabbit tibia and femur. The removal torque and histology were compared after 6 weeks *in situ*. It was reported that (i) no qualitative or quantitative differences were detected for implants with different preoperative preparation and (ii) the conventional implant treatment described is sufficient to give a surface condition with similar early healing response as those observed with glow-discharge treated implants. Buser et al. [114] treated CpTi surface by sand blasting, acid treatment in $\text{HCl}/\text{H}_2\text{SO}_4$, and the HA coating. It was reported that (i) rough implant surfaces generally demonstrated an increase in bone apposition compared to polished or fine-structured surfaces, (ii) the acid-treated CpTi implants had an additional stimulating influence on bone apposition, (iii) the HA-coated implants showed the highest extent of bone–implant interface, and (iv) the HA coating consistently revealed signs of resorption [114].

Generally, roughened surfaces have been used as the endosseous area of a dental implant in order to increase the effective total area available for osseointegration. However, there is still considerable controversy concerning the optimal surface geometry and physicochemical properties for the ideal endosseous portion of a dental implant. Knabe et al. [115] used rat bone marrow cells to evaluate different Ti and HA dental implant surfaces. The implant surfaces were a Ti surface having a porous Ti plasma-sprayed coating, a Ti surface with a deep profile structure, an uncoated Ti substrate with a machined surface, and a machined Ti substrate with a porous HA plasma-sprayed coating. Rat bone marrow cells were cultured on the disk-shaped test substrates for 14 days. The culture medium was changed daily and examined for Ca and P concentration. It was reported that (i) all tested substrates facilitated rat bone marrow cell growth of extracellular matrix formation, (ii) Ti surfaces with a deep profile structure and with porous Ti plasma-sprayed coating to the highest degree, followed by machined Ti and Ti with porous HA plasma-sprayed coating, (iii) Ti surfaces with a deep profile structure and with porous Ti plasma-sprayed coating displayed the highest cell density, and thus seems to be well suited for the endosseous portion of dental implants, and (iv) the rat bone marrow cells cultured on Ti with porous HA plasma-sprayed coating showed a delayed growth pattern due to high phosphate ion release [115].

The modern range of medical devices presents contrasting requirements for adhesion in biological environments. For artificial blood vessels, the minimum adhesion of blood is mandatory, whereas the maximum blood cell adhesion is required at the placed implant surface. Strong bioadhesion is desired in many circumstances to assure device retention and immobility. Minimal adhesion is absolutely essential in others, where thrombosis or bacteria adhesion would destroy the utility of the implants. In every case, primary attention must be given to the qualities of the first interfacial conditioning films of biomacromolecules deposited from the living systems. For instance, fibrinogen deposits from blood may assume different configurations on surfaces of different initial energies, and thus trigger different physiological events. Standard surface modification techniques, such as siliconization, when properly quality controlled, can yield improved blood-compatible devices like substitute blood vessels and artificial heart sacs [116,117].

Sunny and Sharma [118] showed that the Ti oxide film on Ti affects the adsorption rate of albumin/fibrinogen significantly. Multinucleated giant cells have been observed at interfaces between bone marrow and Ti implants in mouse femurs, suggesting that macrophage-derived factors might perturb local lymphopoiesis, possibly even predisposing to neoplasia in the B lymphocyte lineage. It has been found that (i) an implant–marrow interface with associated giant cells persists for at least 15 years, (ii) precursor B cells show early increase in number and proliferative activity; however (iii) at later intervals they do not differ significantly from controls. Rahal et al. [119] mentioned, in the mouse study, that following initial marrow regeneration and fluctuating precursor B cell activity, and despite the presence of giant cells, Ti implants apparently become well tolerated by directly apposed bone marrow cells in a lasting state of so-called myelointegration.

Sukenik et al. [120] modified the surface of Ti by covalent attachment of an organic monolayer anchored by a siloxane network. This coating completely covers the metal and allows controlled modifications of surface properties by the exposed chemical end groups of the monolayer forming surfactant. The attachment of such a film allows different bulk materials (e.g., glass and Ti) to have identical surface properties, and this can be used in regulating cell adhesion responses. It was found that (i) this control over surface functionality can modulate the functions of fibronectin in regulating attachment and neurite formation by neuronal cells and (ii) the effect on bacteria adherence that is achieved by using such monolayers to vary surface hydrophilicity is also assessed [120].

Cell adhesion is involved in various natural phenomena such as embryogenesis, maintenance of tissue structure, wound healing, immune response, and metastasis, as well as tissue integration of biomaterial [121]. The biocompatibility of biomaterials is very closely related to cell behavior on contact with them, and particularly to cell adhesion to their surface. Surface characteristics of materials (whether their topography, chemistry, or surface energy) plays an essential part in osteoblast adhesion on biomaterials. Thus, attachment, adhesion, and spreading belong to the first phase of cell–material interactions, and the quality of this first phase will influence the cell's capacity to proliferate and to differentiate itself on contact with the implant. It is essential for the efficacy of orthopedic or dental implants to establish a mechanically solid interface with complete fusion between the materials' surface and the bone tissue with no fibrous interface, as mentioned previously. Moreover, the recent development of tissue engineering in the field of orthopedic research makes it possible to envisage the association of autologous cells and/or proteins that promote cell adhesion with osteoconductive material to create osteoinductive materials or hybrid materials. Thus, a complete understanding of the cell adhesion, and particularly osteoblast adhesion on materials, is now essential to optimize the bone–biomaterial interface at the heart of these hybrid materials [121].

Dmytryk et al. [122] examined the ability of tissue culture fibroblasts to attach and colonize on the surface of CpTi dental implants following instrumentation of the implant surface with currettes of dissimilar composition. CpTi dental implants were scaled with a plastic, Ti–6Al–4V alloy, or stainless steel curette and then immersed in a cell suspension of 3T3 fibroblasts. Counts of attached cells were made at 24 and 72 h; the implants were then processed for SEM. At 24 h, only surfaces scaled with a stainless steel curette showed a significant reduction in the number of attached cells relative to untreated control surfaces. It was found that, at 72 h, both stainless steel and Ti–6Al–4V alloy curette instrument surfaces showed significantly fewer attached cells than untreated control surfaces, with the greatest reduction in cell attachment observed on stainless steel curette instrument surfaces [122]. Ryhänen et al. [123] evaluated the new bone formation, modeling, and cell–material interface responses induced by the NiTi SME alloy after periosteal implantation. The regional acceleratory phenomenon (RAP) model was employed, in which a periosteal contact stimulus provokes an adaptive modeling response. The test implant was placed in contact with the intact femur periosteum, but it was not fixed inside the bone. It was found that (i) a typical periimplant bone wall

modulation was seen due to the normal RAP, (ii) the maximum new woven bone formation started earlier (2 weeks) in the Ti–6Al–4V group than the NiTi group but also decreased earlier, and at 8 weeks the NiTi and stainless steel groups had greater cortical bone width, and (iii) at 12 and 26 weeks, no statistical significances were seen in the histomorphometric values. Based on these findings, it was concluded that NiTi had no negative effect on total new bone formation or normal RAP after periosteal implantation during a 26-week follow-up [123]. The bone formation around CpTi implants with varied surface properties was tested by Larsson et al. [124]. Machined and electropolished CpTi samples with and without anodically formed surface oxides were prepared and inserted into the cortical bones of rabbits (1, 3, and 6 weeks). It was reported that (i) after 1 week, the smooth, electropolished implants, irrespective of anodic oxidation, were surrounded by less bone than the machined implants, (ii) after 6 weeks, the bone volume as well as the bone–implant contact was lower for the merely electropolished implants than for the other three groups; however (iii) the result with the smooth (electropolished) implants indicates that a reduction of surface roughness, in the initial phase, decreases the rate of bone formation in rabbit cortical bone [124]. Larsson et al. [125], in another experimental study, analyzed the bone formation around systematically modified CpTi implants which were machined, electropolished, and anodically oxidized, and were inserted in the cortical bone of rabbits (7 and 12 weeks). It was found that (i) light microscopy revealed that all implants were in contact with bone, and a large proportion of bone within the threads and (ii) the smooth, electropolished implants were surrounded by less bone than the machined implants with similar oxide thickness (4–5 nm) and the anodically oxidized implants with 21–180 nm after 7 weeks. It was further reported that a high degree of bone contact and bone formation could be achieved with CpTi implants which are modified with respect to oxide thickness and surface topography; however, it appears that a reduction of surface roughness may influence the rate of bone formation in rabbit cortical bone [125]. Since interactions among cell/matrix/substrate, which are associated with cell signaling, occur in the nanoscale dimension, Oliveira and Nanci [126] evaluated the influence of nanotexturing of Ti-based surfaces (CpTi and Ti–6Al–4V, treated by H₂SO₄ and 30% H₂O₂) on the expression of matrix proteins by cultured osteogenic cells at initial time points. It was reported that (i) after 6 h, nanotextured surfaces exhibited up to a ninefold increase in the proportion of cells with peripheral osteopontin labeling, (ii) at day 3, the proportion of osteopontin and bone sialoprotein-labeled cells was higher, and the intensity of immunoreactivity dramatically increased, and (iii) no significant differences were observed in the expression pattern and the proportion of cells immunoreactive for fibronectin [126].

Biological performance of dental and orthopedic implants depends on factors such as composition, design, surface topography, sterilization, and surgical technique. Common dental implants are made of different grades of CpTi. Ahmad et al. [127] conducted *in vitro* tests to determine whether human osteoblast-like cells (Saos-2) would respond differently to disks of CpTi (grades 1 and 4), compared to glass disks serving as controls. It was reported that (i) rhodamine phalloidin fluorescence microscopy showed variations in the actin-based cytoskeleton between

grades 1 and 4 CpTi in cell spreading, shape, and the organization of stress fibers, (ii) immunofluorescent staining showed differential expression of vinculin, a focal adhesion protein, on the substrates, (iii) at 24 h, the percent of collagen synthesized was significantly more on grade 1 than on grade 4 and on glass, and (iv) the calcium content was significantly higher on grade 1 than on grade 4 and on glass at 24 h and at 4 weeks. It was, thus, concluded that commonly used CpTi induced differential morphologic and phenotypic changes in human osteoblast-like cells depending on the grade of the material [127]. The spreading and orientation of human gingival fibroblasts in relation to the rim of smooth-surfaced and porous-coated Ti disks was *in vitro* investigated. It was found that (i) the cells migrated from the multilayer onto the smooth-surfaced disks forming bridges between them and orientated along parallel circumferential grooves in the rim of the disks and (ii) cellular bridges were also formed between the porous-coated disks and the multilayer, but because the cells that migrated onto and between the sphere of the porous coated showed no preferred orientation, the bridges retained their orientation at right angles to the surface of the rim. This suggests that the geometrical configuration of the surface of the implants could influence whether a capsule or an orientated fibrous attachment is developed in relation to implants *in vivo* [128].

Proliferation and adhesion of mouse osteoblastic cells and primary osteoblastic cells were carried out on Ti–6Al–4V samples with varied surface roughness [129]. Mechanically or manually polished surfaces were prepared to produce, respectively, nonorientated or orientated polishing grooves. Sand-blasted surfaces were prepared using 500- μm or 3-mm alumina particles. It was found that (i) surface roughness parameters showed a negative correlation in comparison to proliferation and adhesion parameters and (ii) X-ray microprobe chemical microanalysis showed complete disturbance of the surface element composition of the Ti–6Al–4V following sand-blasting treatment on which an AlO_x -enriched layer was observed. This may lead to the suspicion that the concomitant effect of surface roughness amplitude and AlO_x surface concentration has an effect on osteoblastic cell proliferation and adhesion. It was demonstrated that usual surface preparation for increasing the bone integration of Ti–6Al–4V surgical implants (i.e., sand-blasting) may extensively transform their chemical surface composition. Therefore, the expected bone integration of implants may be extensively impaired by surface treatments [129]. The possible contamination by used blasting media on Ti surfaces will be discussed in Chapter 11. Mustafa et al. [130] analyzed variations in the oxide films on CpTi surfaces blasted with TiO_2 particles of various sizes after cultures with cells derived from human mandibular bone. Turned Ti surfaces and sand blasted with 63–90, 106–180, and 180–300- μm TiO_2 particles were cultured with osteoblast-like cells. The surfaces were characterized before and after the cell culture with EIS. It was found that (i) EIS revealed, with respect to the turned surfaces, the effective surface area was about 5, 6, and 4 times larger on the surfaces blasted with 63–90, 106–180, 180–300 μm particles, respectively, (ii) after 28 days of the cell culture, the corrosion resistance on all sample types was unaffected; the impedance characteristics suggest a considerable effect of ion incorporation and precipitation during culturing, (iii) XPS revealed that before the cell

culture, a typical surface layer consisted of TiO_2 , and (iv) after the culture, the surface oxide film contained both P and Ca, along with large amounts of oxidized carbon (carbonate) and nitrogen [130]. Lee et al. [131] examined the cell attachment and proliferation of neonatal rat calvarial osteoblasts on Ti–6Al–4V as affected by the surface modifications (as polished, heated in vacuum at 970°C for 8 h to have $300\text{ }\mu\text{m}$ thick brazed, at 970°C for 8 h to have $600\text{ }\mu\text{m}$ brazed). During the brazing, a foil of Ti–15Cu–15Ni with melting point of 934°C was placed top of the Ti–6Al–4V. All samples were passivated by boiling them in distilled water for 24 h, followed by autoclaving at 121°C for 15 min. The modifications could alter simultaneously the surface chemistries of the alloy, as well as the surface characteristics of oxides on the metal. It was found that a slight change of the surface characteristics of oxides as a result of the modifications neither alters the *in vitro* capacity of Ca and P ion adsorption nor affects the metal ion dissolution behavior of the alloy, suggesting that any influence on the cytocompatibilities of the materials should only be correlated to the effect of surface chemistries of the alloy and the associated metal ion dissolution behavior of the alloy. It was therefore concluded that the cell response of neonatal rat calvarial osteoblasts on the Ti–6Al–4V alloy should not be affected by the variation of surface chemistries of the alloy in a range studied [131]. To investigate the roles of compositions and properties of Ti surface oxides in cellular behavior of osteoblasts, the surface oxides of Ti were modified in composition and topography by anodic oxidation in two kinds of electrolytes, 0.1 M H_3PO_4 and a mixture of 0.03 M calcium glycerophosphate and 0.15 M calcium acetate. It was found that (i) phosphorous (P: about 10 at.%) or both Ca (1–6 at.%) and P (3–6 at.%) were incorporated into the anodized surfaces in the form of phosphate and calcium phosphate and (ii) contact angles of all the anodized oxides were in the range of $60\text{--}90^\circ$, indicating relatively high hydrophobicity. It was also mentioned that cell culture experiments demonstrated absence of cytotoxicity and an increase of osteoblast adhesion and proliferation by the anodic oxides [132].

Bony ingrowth to control (nontreated) and heat-treated (autoclaved at 280°C for 3 h) stainless steel and Ti–6Al–4V implants into the medullary canal of the femur in rats was studied by Hazan et al. [133]. It was found that (i) at all time intervals up to 3 days postimplantation, the shear strengths of heat-treated Ti–6Al–4V and stainless steel implants were significantly higher (1.6-fold and 3.4-fold) than the controls and (ii) the heat treatment of metal implants prior to their insertion alters their chemical surface properties and augments bony ingrowth to them [133]. Characteristics of the porous surfaces may be important in improving the bone ingrowth into the porous coatings. Quicker and more mature interstitial bone formation was obtained using a porous rather than a solid structure due to differences of penetration by some growth factors and bone marrow cells [134–136]. Li et al. [137] examined the effect of the surface macrostructure of a dimpled CpTi implant on bone ingrowth *in vivo* by means of histological examination and a push-out test. Dimples had diameters of 100, 140, and $160\text{ }\mu\text{m}$, and distance between dimple centers of about $400\text{ }\mu\text{m}$. Cylindrical implants were inserted in rabbits for 1.5, 3, and 13 months. The femur with the implant of each animal was then examined in a

push-out test. It was found that the dimpled CpTi surface results in an increased retention of the implant in bone due to interlocking between vital bone and the dimples [137].

NiTi SME alloy makes it possible to prepare functional implants that apply a continuous benign force to the bone. Kujala et al. [138] investigated if bone modeling can be controlled with a functional intramedullary NiTi nail. Preshaped NiTi nails with a curvature radius of 25–37 mm were implanted in the cooled martensite phase form in the medullary cavity of the right femur in 8 rats, where they restored their austenite form, causing a bending force. After 12 weeks, the operated femurs were compared with their nonoperated contralateral counterparts. It was found that (i) quantitative densitometry showed a significant increase in the average cross-sectional cortical area and cortical thickness, which were most obvious in the mid-diaphyseal area, (ii) cortical bone mineral density increased in the proximal part of the bone and decreased in the distal part, and (iii) polarized light microscopy of the histological samples revealed that the new bone induced by the functional intramedullary nail was mainly woven bone. It was, therefore, concluded that bone modeling can be controlled with a functional intramedullary nail made of NiTi SME alloy [138]. The biocompatibility of NiTi as a potential implant material was investigated through *in vivo* studies on beagles. A high-purity alloy was fabricated into prototype bone plates and implanted into the femurs of beagles. Commercial Co–Cr alloy bone plates served as reference controls. The bone plates were removed from the animals and examined after exposures of 3, 6, 12, and 17 months. It was reported that (i) there was no evidence of localized or generalized corrosion on the surfaces of the bone plates and screws, (ii) gross clinical, radiological, and morphological observations of the tissue at the implantation sites during the autopsies uncovered no signs of adverse tissue reactions resulting from the implants, and (iii) a histological analysis was performed on samples of muscle and bone adjacent to the implantation sites and of tissues removed from such organs as the liver, spleen, brain, and kidneys. It was further found that there was no metallic contamination in the organs due to the implants; however, there does appear to be some chromium contamination from the Co–Cr alloy implants in the adjacent bone, and concluding that NiTi alloy is sufficiently compatible with dog tissue to warrant further investigation of its potential as a biomaterial [139].

Nishiguchi et al. [140] evaluated the bone-bonding ability of three differently treated samples of CpTi: (1) as a smooth surface control, (2) treated in 5 M NaOH solution for 24 h at 60°C, and (3) heated at 600°C for 1 h. The plates were inserted transcortically into the proximal metaphyses of bilateral rabbit tibiae. The tensile failure loads between implants and bones were measured at two intervals using a detaching test. It was reported that (i) the tensile failure loads of the alkali- and alkali-heat-treated group were 27 and 40 MPa, at 8 and 16 weeks, and significantly higher than those of the other Ti groups, (ii) histological examination revealed that alkali- and heat-treated Ti were in direct contact with bone, but the other Ti groups had a thin intervening fibrous tissue, and (iii) the alkali-treated Ti without heat treatment had no bone-bonding ability due to the unstable reactive surface layer of alkali-treated Ti. It was therefore concluded that both alkali and heat treatment are

essential for preparing bioactive Ti, and this bioactive Ti is thought to be useful for orthopedic implants with cementless fixation [140].

There is an increasing attention given to the influence of surface condition and in particular on methods to control and improve titanium implant surfaces; such techniques should include laser surface treatment [141], strain hardening [142] and chemical passivation methods [143]. From histological examinations, it has been found that implant loosening is generally associated with the formation of fibrous tissue at the bone–implant interface. To improve implant biocompatibility and osteointegration, Ti–6Al–4V alloy was treated by passivation by immersion in 30% HNO_3 for 1 h, or passivation in boiling distilled water for 10 h [142], resulting in an increase in the oxide layer thickness of Ti–6Al–4V alloy as orthopedic implant material. The kinetics of gene expression over 120 h was followed for 58 genes to quantify the effect of the developed surface treatment. Twenty-eight genes were further selected to compare the effects of surface treatments on osteoblasts. Based on the genes studies, a general pathway for the cell reaction was proposed according to the surface treatment used: (1) metal ion release changes the time course of gene expression in the focal adhesion kinase pathway; (2) once the accumulation of metal ions released from the Ti surface exceeds a threshold value, cell growth is diminished and apoptosis may be activated; (3) protein tyrosine kinase up-regulation is also induced by metal ion release; (4) expression of the Bcl-2 family and Bax may suggest that metal ions induce apoptosis [144].

The cleanliness of Ti dental implant surfaces is considered to be important for achieving osseointegration, and it has been hypothesized that the presence of inorganic contaminants could lead to a lack of clinical success. Anselme et al. [129] pointed out that aluminum ions are suspected of impairing bone formation by a possible competitive action to calcium. Piattelli et al. [145] investigated the effects of residual Al_2O_3 particles on the implant surface on the integration of Ti dental implants as compared to decontaminated implants in a rabbit experimental model. Threaded screw-shaped machined grade 3 CpTi dental implants were used. The implants were sand blasted with 100–120 μm Al_2O_3 particles at 1.5 atm pressure for 1 min; 24 implants (control implants) underwent the ASTM 86-68 decontamination process in an ultrasonic bath. The other 24 implants (test implants) were washed in saline solution for 15 min. Both test and control implants were air dried and sterilized at 120°C for 30 min. After sterilization, the implants were inserted into the tibiae of New Zealand white mature rabbits. All animals were euthanized after 4 weeks. A total of 48 implants were retrieved. It was found that (i) percentage of the implant surface covered by inorganic particles was significantly higher than that of control implants, (ii) no statistically significant differences were found in the bone–implant contact percentage of test and control implants, and (iii) no differences were found in the number of multinucleated cells and osteoblasts in contact with the implant surface. Hence, it was concluded that histological results do not provide evidence to support the hypothesis that the residual aluminum oxide particles on the implant surface could affect the osteointegration of Ti dental implants [145].

Primary stability and an optimized load transfer are assumed to account for an undistributed osteointegration process of implants. Immediate loading type newly

designed Ti dental implants inserted in the mandible of minipigs were used for the characterization of the interface area between the implant surface and the surrounding bone tissue during the early healing phase. Histological and SEM studies were done. Two different load regimes were applied to test the load-related tissue reaction. It was shown that (i) a direct bone apposition on the implant surfaces as well as the attachment of cells and matrix protein in the early loading phase and (ii) a striking finding of the ultrastructural immunocytochemical investigations were the synthesis and deposition of bone proteins (osteonectin, fibronectin, fibronectin receptors) by osteoblasts from day one of bone/biomaterials interaction. It was, therefore, suggested that loadings of specially designed implants can be performed immediately after insertion without disturbing the biological osteointegration process [146]. Apatite formation on implants is important in achieving a direct bonding to bone tissue. It was shown that a Ti surface that was chemically treated with a H_2O_2 solution containing tantalum chloride had the ability to form a HA layer in simulated body fluid (SBF) that had an inorganic ion composition similar to human blood plasma [147]. A CpTi cylinder treated with a H_2O_2 solution with tantalum chloride was inserted into a hole in a rabbit's tibia for 16 weeks. It was found that (i) 8 weeks after surgery, the shearing force of the treated Ti implanted in the 4.2 mm hole was significantly higher than that of the nontreated Ti, although the surface roughness was not changed after the treatments and (ii) the shearing force was higher for the implanted sample in the 4.0 mm hole than that in the 4.2 mm hole [147].

Recently Gil et al. [148] determined whether the mechanical properties of titanium dental implants changed after exposure to bacteria. Two strains of bacteria (*Streptococcus sanguinis* and *Lactobacillus salivarius*) were used. The adhesive properties of the two strains were investigated as follows. Titanium implants were placed in bacteria broth, seeded with the two bacteria strains, and left in the broth for 1 or 3 months. Another group of titanium implants was immersed in artificial saliva at 37°C for 3 months. Ten implants in each group were tested in 37°C artificial saliva to evaluate their mechanical strength and fatigue life. The bacteria cultures grew quickly on titanium surfaces. After 3 months of bacteria culture, a 7% decrease in the flexural strength of the implant samples and a 1% decrease in the number of cycles failed by fatigue were seen versus implants not exposed to bacteria. These results demonstrate that, in physiologic conditions *in vitro*, bacteria have the capacity to produce a pitting corrosion phenomenon on exposed titanium surfaces, leading to a significant deterioration in the mechanical properties of the implant. It is, therefore, logical to conclude that bacteria may produce corrosion that reduces the useful life of dental implants. These results confirm what the present author had published on electrochemical study on microbiology-related corrosion of various titanium materials in media containing *S. mutans* strain [149].

8.7 Surface Modification Effects

In order to enhance the surface hardness of titanium materials, there are several methods proposed and developed to diffuse interstitial elements (nitrogen, oxygen,

and boron) into titanium crystal matrix [150]. These interstitial elements react with Ti to form hard and wear-resistant compound layers at the surface and thereby enhance the wear/abrasion properties.

Surface roughness appears to be a very effective feature of a titanium implant surface [151,152]. Cell proliferation and extracellular matrix formation are primary events in bone formation. At the dental implant–tissue interface, implant surface roughness modulates osteoblast functions. The aim of this study was to investigate the effect of varying surface roughness of titanium implant material on cell proliferation and mRNA expression of specific markers of osteoblast phenotypes. It was found that human osteoblasts cultured on machined titanium spread more and were flatter than cells cultured on rough titanium. All blasted surfaces showed significantly higher DNA synthesis than the machined surfaces. Osteonectin mRNA expression was similar on all surfaces. It was concluded that an average surface roughness of 3 μm (macro-sand-blasted Ti) is more suitable than an average surface roughness of 0.5 μm (microsand-blasted Ti) in favoring osteoblast differentiation *in vitro* [151]. Some of the critical properties for a successful orthopedic or dental implant material are its biocompatibility and bioactivity. Pure Ti and Zr are widely accepted as biocompatible metals, due to their nontoxicity. While the bioactivity of Ti and some Ti alloys has been extensively investigated, there is still insufficient data for Zr and Ti–Zr alloys. The bioactivity, that is, the apatite-forming ability of the alkali and heat-treated surfaces of Ti, Zr, and TiZr alloy in SBF, was studied. In particular, the effect of the surface roughness characteristics on the bioactivity was evaluated for the first time. The results indicate that the pretreated Ti, Zr, and TiZr alloy could form apatite coatings on their surfaces. It should be noted that the surface roughness also critically affected the bioactivity of these pretreated metallic samples. A surface morphology with an average roughness of approximately 0.6 μm led to the fastest apatite formation on the metal surfaces. This apatite layer on the metal surface is expected to bond to the surrounding bones directly after implantation [152]. The osteogenic potential of CpTi was evaluated after different surface treatments. Thirty CpTi (grade II) disks were divided into three groups. In the first group (group C), polished samples were used as the control group. In the second group (group SG), an oxide layer was coated on the samples using a sol–gel dip technique. In the third group (group SA), samples were sand blasted and treated with different acids in succession to etch the samples. The SA and SG surfaces were rougher than that of control group. There was a significant increase in oxygen content in groups SG and SA. Cell sheets were able to penetrate into the pores and adhered inside the valleys of the SA samples, suggesting excellent attachment [153]. The surface characteristics and bone response of titanium implants produced by hydrothermal treatment using H_3PO_4 was investigated and compared to those of implants produced by commercial surface treatments—machining, acid etching, grit blasting, grit blasting/acid etching, or spark anodization. The osteoconductivity was evaluated by removal torque testing and histomorphometric analysis after 6 weeks of implantation in rabbit tibiae. Hydrothermal treatment with H_3PO_4 and subsequent heat treatment produced a crystalline phosphate ion-incorporated oxide

(titanium oxide phosphate hydrate, $\text{Ti}_2\text{O}(\text{PO}_4)_2(\text{H}_2\text{O})_2$; TiP) surface approximately $5\text{ }\mu\text{m}$ in thickness, which had needle-like surface microstructures and superior wettability compared with the control surfaces. Significant increases in removal torque forces and bone-to-implant contact values were observed for TiP implants compared with those of the control samples. After thorough cleaning of the implants removed during the removal torque testing, a considerable quantity of attached bone was observed on the surfaces of the TiP implants [154]

References

- [1] Brown D. Dental implants. *Mater World* 1996;4:259–61.
- [2] Brockhurst PJ. Dental materials: new territories for materials science. *Met Forum Aust Inst Metals* 1980;3:200–10.
- [3] Binon PP. Implants and components: entering the new millennium. *Int J Oral Maxillofac Implants* 2000;15:76–94.
- [4] ICOI—International congress of oral Implantologists. <<http://icoi.org/implant-manufacturers-list.php>>.
- [5] Carr D, Oshida Y, Platt JA, Barco MT, Hovijitra S, Andres CJ. Effects of pre-fatigue damage on remaining cement bond strength in a cement-retained Cera-One implant system. In: Shrivastava S, editor. *Medical device materials, proceedings materials and processes for medical devices conference*. Materials Park, OH: ASM International; 2003. p. 463–6.
- [6] Carr D, Oshida Y, Platt JA, Barco MT, Andres CJ. The effect of fatigue damage on the force required to remove a restoration in cement-retained implant system. *J Prosthodont* 2006;15:289–94.
- [7] Rostoker W, Galante JO. The influence of titanium surface treatments on the wear of medical grade polyethylene. *Biomaterials* 1981;2:221–4.
- [8] Bannon BP, Mild EE. Titanium alloys for biomaterial application: an overview. In: Luckey HA, Kubli F, editors. *Titanium alloys in surgical implants*. ASTM STP 796; 1983. p. 7–15.
- [9] Long M, Rack HJ. Review: titanium alloys in total joint replacement—a materials science perspective. *Biomaterials* 1998;19:1621–39.
- [10] Brunski JB, Puleo DA, Nanci A. Biomaterials and biomechanics of oral and maxillofacial implants: current status and future developments. *Intl J Oral Maxillofac Implants* 2000;15:15–46.
- [11] Carlos CS. Osteoarthritis/Osteoarthritis concepts. <<http://www.cvm.umn.edu/academics>>.
- [12] Curtis R. Superplastic forming of dental implants. *Mater World* 1999;10:607–9.
- [13] Oshida Y, Barco MT. Superplastically-formed prosthetic components, and equipment for same. US Patent 6,116,070; 2003.
- [14] Al Jabbari Y, Nagy WW, Iacopino AM. Implant dentistry for geriatric patients: a review of the literature. *Quint Int* 2003;34:281–5.
- [15] Ship JA, Chavez EM. Management of systemic diseases and chronic impairments in older adults: oral health consideration. *Gen Dent* 2000;48:557–8.
- [16] Oshida Y. Requirements for successful biofunctional implants. *Int Symp Adv Biomater* 2000;5.

- [17] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones: toward a morphological compatibility of implants. *J Biomed Mater Eng* 1994;4:397–407.
- [18] Edwards BN, Gold BR. Analysis of surface cleanliness of three commercial dental implants. *Biomaterials* 1992;13:775–80.
- [19] Granström G. Craniofacial osseointegration. *Oral Dis* 2007;13:261–9.
- [20] Bencharit S. Challenges and prospective applications of extra-oral implants for maxillofacial rehabilitation. *Anaplastology* 2012;1:103–4.
- [21] Abu-Serriah MM, McGowan DA, Moos KF, Bagg J. Outcome of extra-oral craniofacial endosseous implants. *Br J Oral Maxillofac Surg* 2001;39:269–75.
- [22] Karakoca S, Aydin C, Yilmaz H, Bal BT. Survival rates and periimplant soft tissue evaluation of extraoral implants over a mean follow-up period of three years. *J Prosthet Dent* 2008;100:458–64.
- [23] Curi MM, Oliveria MF, Molina G, Cardoso CL, De Groot Oliveira L, Brånemark P-I, et al. Extraoral implants in the rehabilitation of craniofacial defects: implant and prosthesis survival rates and peri-implant soft tissue evaluation. *J Oral Maxillofac Surg* 2012;70:1551–7.
- [24] Arcuri M, LaVelle W, Higuchi KW, Hofman HH. Combined percutaneous-permucosal titanium implants for retention of a maxillary prosthesis: a clinical report. *J Prosthet Dent* 1993;70:288–90.
- [25] Goiato MC, Dos Santos DM, Haddad MF, Moreno A. Rehabilitation with ear prosthesis linked to osseointegrated implants. *Gerodontology* 2012;29:150–4.
- [26] Wolfaard J, Gehl G, Farman M, Wilkes G. Indications and methods of care for aspects of extraoral osseointegration. *Int J Oral Maxillofac Surg* 2003;32:124–31.
- [27] Federspil P, Bull HG, Federspil PA. Epithetische Wiederherstellung im Gesicht. *Dt Äztebl* 1998;95:A206–13.
- [28] Sharp I, Jeynes P, Waheed U, Pamar S, Martin T, Worrollo S. Craniofacial implants for extra-oral prosthetic reconstruction. *Int J Oral Maxillofac Surg* 2007;36:1055–62.
- [29] Pekkan G, Tuna SH, Oghan F. Extraoral prostheses using extraoral implants. *Int J Oral Maxillofac Surg* 2011;40:378–83.
- [30] Sinn DP, Bedrossian E, Vest AK. Craniofacial implant surgery. *Oral Maxillofac Surg Clin* 2011;23:321–35.
- [31] Granström G. Craniofacial osseointegration. *Oral Dis* 2007;13:261–9.
- [32] Seelaus R, Troppmann RJ. Facial prosthesis fabrication: coloration techniques. In: Taylor, editor. *Clinical maxillofacial prosthetics*. Chicago: Quintessence; 2000. p. 245–64.
- [33] Troppmann RJ, Wolfaardt JF, Grace M, James A. Spectrophotometry and formulation of coloring facial prosthetic silicone elastomer: a pilot clinical trial. *J Facial Somato Prosthet* 1996;2:85–92.
- [34] Adell R, Eriksson B, Lekholm U, Brånemark P-I, Jemt T. A long-term follow-up study of osseointegrated implants in the treatment of totally edentulous jaws. *Intl J Oral Maxillofac Implants* 1990;5:347–59.
- [35] TuftsOpenCourseWare. <<http://ocw.tufts.edu/courses/10/content/2446.58>>.
- [36] Åstrand P, Borg K, Gunne J, Olsson M. Combination of natural teeth and osseointegrated implants as prosthesis abutments: a 2-year longitudinal study. *Intl J Oral Maxillofac Implants* 1991;6:305–12.
- [37] Kohavi D, Schwartz Z, Amir D, Mai CM, Gross U, Sela J. Effect of titanium implants on primary mineralization following 6 and 14 days of rat tibial healing. *Biomaterials* 1992;13:255–60.

- [38] Piattelli A, Corigliano M, Scarano A. Microscopical observations of the osseous responses in early loaded human titanium implants: a report of two cases. *Biomaterials* 1996;17:1333–7.
- [39] Saadoun AP, Le Gall MG. An 8-year complication of clinical results obtained with Steri-oss endosseous implants. *Compendium* 1996;17:669–80.
- [40] Piattelli A, Scarano A, Nora AD, De Bona G, Favero GA. Microscopical features in retrieved human Brånemark implants: a report of 19 cases. *Biomaterials* 1998;19:643–9.
- [41] Cochran DL. The scientific basis for and clinical experiences with Straumann implants including the ITI® Dental implant system: a consensus report. *Clin Oral Implants Res* 2000;11:33–58.
- [42] Leonhardt Å, Gröndahl K, Bergström C, Lekholm U. Long-term follow-up of osseointegrated titanium implants using clinical, radiographic and microbiological parameters. *Clin Oral Implants Res* 2002;13:127–32.
- [43] Cochran DL, Buser D, ten Bruggenkate CM, Weingart D, Taylor TM, Bernard JP, et al. The use of reduced healing times on ITI® implants with a sandblasted and acid-etched (SLA) surface: early results from clinical trials on ITI® SLA implants. *Clin Oral Implants Res* 2002;13:144–53.
- [44] Meijer HJA, Raghoobar GM, Van't Hof MA, Visser A. A controlled clinical trial of implant-retained mandibular overdentures: 10 years' results of clinical aspects and aftercare of IMZ implants and Brånemark implants. *Clin Oral Implants Res* 2004;15:421–7.
- [45] Ichinose S, Muneta T, Aoki H, Tagami M. TEM observation of seven retrieved total knee joints made of Co–Cr–Mo and Ti–6Al–4V alloys. *J Biomed Mater Eng* 2003;13:125–34.
- [46] Goodacre CJ, Bernal B, Rungcharassaeng K, Kan J. Clinical complications with implants and implant prostheses. *J Prosthet Dent* 2003;90:121–32.
- [47] Simon RL. Single implant-supported molar and premolar crowns: a ten-year retrospective clinical report. *J Prosthet Dent* 2003;90:517–21.
- [48] Thimmappa B, Girod SC. Principles of implant-based reconstruction and rehabilitation of craniofacial defects. *Craniofacial Trauma Reconstr* 2010;3:33–40.
- [49] Tolman DE, Desjardins RP, Jackson IT, Brånemark P-I. Complex craniofacial reconstruction using an implant-supported prosthesis: case report with long-term follow-up. *Int J Oral Maxillofac Implants* 1997;12:243–51.
- [50] Flood TR, Russel K. Reconstruction of nasal defects with implant-retained nasal prostheses. *Br J Oral Maxillofac Surg* 1998;36:341–5.
- [51] Proissaefs P. Use of frontal process of the maxillary bone for implant placement to retain a nasal prosthesis: a clinical report. *Int J Oral Maxillofac Implants* 2004;19:901–5.
- [52] Lovely M, Munirathnam Naidu E, Chandrasekharan Nair K, Subramoniam R, Komath M, Varma HK. Design and development of an implant system for auricular prosthesis. *Trends Biomater Artif Organs* 2010;24:11–8.
- [53] Gumieiro EH, Dib LL, Jahn RS, dos Santos Junior JF, Nannmark U, Granström G, et al. Bone-anchored titanium implants for auricular rehabilitation: case report and review of literature. *Sao Paulo Med* 2009;127:160–5.
- [54] Salina T. Prosthetic rehabilitation of defects of the head and neck. *Semin Plast Surg* 2010;24:299–308.
- [55] Alberto PL. Implant reconstruction of the jaw and craniofacial skeleton. *Mt Sinai J Med* 1998;65:316–21.

- [56] Cervelli V, Migliano E, Giudiceandrea F, Grimaldi M, Cervelli G. Titanium bone-integrated implants in extraoral facial prosthetic rehabilitation: surgical planning and long-term follow-up. *Eur Rev Med Pharmacol Sci* 1997;2:207–12.
- [57] Goodman A. Facial prosthetics: an evolving field. *ENT Today* 2009;February:1–9.
- [58] Goiato MC, dos Santos DM, Daniela M, de Carvalho Dekon SF, Pellizzer EP, Santiago JF, et al. Craniofacial implants success in facial rehabilitation. *J Craniofac Surg* 2011;22:241–2.
- [59] Federspil PA. Implant-retained craniofacial prostheses for facial defects. *GMA Curr top Otorhinolaryngol Head Neck Surg* 2011;8:55 [Abstract only].
- [60] Ratner BD, Johnston AB, Lenk TJ. Biomaterial surfaces. *J Biomed Mater Res Appl Biomater* 1987;21:59–90.
- [61] Smith DC, Pilliar RM, Chernenky R. Dental implant materials. I. Some effects of preparative procedures on surface topography. *J Biomed Mater Res* 1991;25:1045–68.
- [62] Smith DC, Pilliar RM, Metson JB, McIntyre NS. Dental implant materials. II. Preparative procedures and surface spectroscopic studies. *J Biomed Mater Res* 1991;25:1069–84.
- [63] Kasemo B, Lausmaa J. Biomaterial and implant surfaces: a surface science approach. *Intl J Oral Maxillofac Implants* 1988;3:247–59.
- [64] Lausmaa J, Kasemo B. Surface spectroscopic characterization of titanium implant materials. *Appl Surf Sci* 1990;44:133–46.
- [65] Sutherland DS, Forshaw PD, Allen GC, Brown IT, Williams KR. Surface analysis of titanium implants. *Biomaterials* 1993;14:893–9.
- [66] Tengvall P, Lundstrom I. Physio-chemical considerations of titanium as a biomaterial. *Clin Mater* 1992;9:115–34.
- [67] Sawase T, Hai K, Yoshida K, Baba K, Hatada R, Atsuta M. Spectroscopic studies of three osseointegrated implants. *J Dent* 1998;26:119–24.
- [68] Albrektsson T, Wennerberg A. Oral implant surfaces: part 1—review focusing on topographic and chemical properties of different surfaces and *in vitro* responses to them. *Int J Prosthodont* 2004;17:536–43.
- [69] Albrektsson T, Wennerberg A. Oral implant surfaces: part 2—review focusing on clinical knowledge of different surfaces. *Int J Prosthodont* 2004;17:544–64.
- [70] Oshida Y. Surface characterization and microanalytical studies on TiNi shape memory dental devices. In: Fukuyo S, Sachdeva R, editors. *Perio root implant and medical application of shape memory alloy*. Tokyo: Japan Medical Culture Center; 1992. p. 17–30.
- [71] James RA. The support system and the perigingival defense mechanism of oral implants. *Oral Implantol* 1975;6:270–85.
- [72] Weiss CM. Tissue integration of dental endosseous implants: description and comparative analysis of the fibro-osseous integration and osseous integration system. *J Oral Implantol* 1986;12:169–214.
- [73] Fox WC, Miller MA. Osseo implant for studies of biomaterials using an *in vivo* electro-chemical transducer. *J Biomed Mater Res* 1993;27:763–73.
- [74] Bearinger JP, Orme CA, Gilbert JL. *In situ* imaging and impedance measurements of titanium surfaces using AFM and SPIS. *Biomaterials* 2003;24:1837–52.
- [75] Hirata I. Development of titanium biosensor for surface plasma resonance analysis system. *J Dent Eng* 2005;152:33–5.
- [76] Meredith DO, Riehle MO, Curtis AS, Richards RG. Is surface chemical composition important for orthopaedic implant materials? *J Mater Sci Mater Med* 2007;18:405–13.

- [77] Saber-Samandari S, Berndt CC, Gross KA. Selection of the implant and coating materials for optimized performance by means of nanoindentation. *Acta Biomater* 2011;7:874–81.
- [78] Kadaso D, Gongadze E, Perutková S, Matschegewski C, Ij-Iglic V, Beck U, et al. Mechanics and electrostatics of the interactions between osteoblasts and titanium surface. *Comput Meth Biomech Biomed Eng* 2011;14:469–82.
- [79] Palmquist A, Lindberg F, Emanuelsson L, Brånemark R, Engqvist H, Thomson P. Morphological studies on machined implants of commercially pure titanium and titanium alloy (Ti6Al4V) in the rabbit. *J Biomed Mater Res B* 2009;91:309–19.
- [80] Puckett SD, Taylor E, Raimondo T, Webster TJ. The relationship between the nanostructure of titanium surfaces and bacterial attachment. *Biomaterials* 2010;31:706–13.
- [81] Helgason B, Viceconti M, Rúnarsson TP, Brynjólfsson S. On the mechanical stability of porous coated press fir titanium implants: a finite element study of a pushout test. *J Biomech* 2008;41:1675–81.
- [82] Sidun J, Dabrowski JR. Investigation of osseointegration of porous materials for orthopedic implants. *Acta Mech Slovaca* 2010;14: 78-85 [14 Abstract only].
- [83] Fujisaki K, Tadano S. Strain measurement of pure titanium covered with soft tissue using X-ray diffraction. *J Biomech Eng* 2010;132:233–41.
- [84] Steinmann SG. Corrosion of surgical implants—in vivo and in vitro tests. In: Winter GD, Leray JL, de Groot K, editors. *Evaluation of biomaterials*. New York: John Wiley & Sons; 1980. p. 1–34.
- [85] Kruger J. Fundamental aspects of the corrosion of metallic implants [ASTM STP 684] In: Syrett BC, Acharya A, editors. *Corrosion and degradation of implant materials*. Philadelphia, PA: American Society for Testing and Materials; 1979. p. 107–27
- [86] Greene ND. Corrosion of surgical implant alloys: a few basic ideas. ASTM STP 859. In: Fraker AC, Griffin CD, editors. *Corrosion and degradation of implant materials: second symposium*; 1983. p. 5–10.
- [87] Cook SD. Interface mechanics of porous metal-coated implants. In: Fagan MJ, editor. *Implant prosthodontics: surgical and prosthetic techniques for dental implants*. Chicago: Year Book Medical Publishers; 1990. p. 305–9.
- [88] Brunski JB. Biomechanical factors affecting the bone-dental implant interface. *Clin Mater* 1992;10:153–201.
- [89] Skalak R. Biomechanical considerations in osseointegrated prostheses. *J Prosthet Dent* 1983;49:843–8.
- [90] Hekimoglu C, Anil N, Cehreli MC. Analysis of strain around endosseous implants opposing natural teeth or implants. *J Prosthet Dent* 2004;92:441–6.
- [91] Cook SD, Kay JF, Thomas KA, Jarcho M. Interface mechanics and histology of titanium and hydroxyapatite-coated titanium for dental implant applications. *Intl J Oral Maxillofac Implants* 1987;2:15–22.
- [92] Himmlová L, Dostálová T, Kácovský A, Konvičková S. Influence of implant length and diameter on stress distribution: a finite element analysis. *J Prosthet Dent* 2004;91:20–5.
- [93] Browne M, Langley RS, Gregson PI. Reliability theory for load-bearing biomedical implants. *Biomaterials* 1999;20:1285–92.
- [94] Sadowky SJ, Caputo AA. Stress transfer of four mandibular implant overdenture cantilever designs. *J Prosthet Dent* 2004;92:328–36.
- [95] van Rossen IP, Braak LH, de Putter C, de Groot K. Stress-absorbing elements in dental implants. *J Prosthet Dent* 1990;64:198–205.
- [96] Rangert B, Gunne J, Sullivan DY. Mechanical aspects of a Brånemark implant connected to a natural tooth: an in vitro study. *Intl J Oral Maxillofac Implants* 1991;6:177–86.

- [97] Lang LA, Kang B, Wang R-F, Lang BR. Finite element analysis to determine implant preload. *J Prosthet Dent* 2003;90:539–46.
- [98] Yokoyama K, Ichikawa T, Murakami H, Miyamoto Y, Asaoka K. Fracture mechanisms of retrieved titanium screw thread in dental implant. *Biomaterials* 2002;23:2459–65.
- [99] Kohn DH, Ducheyne P. A parametric study of the factors affecting the fatigue strength of porous coated Ti–6Al–4V implant alloy. *J Biomed Mater Res* 1990;24:1483–501.
- [100] Kohn DH, Ducheyne P, Awerbuch J. Acoustic emission during fatigue of porous-coated Ti–6Al–4V implant alloy. *J Biomed Mater Res* 1992;26:19–38.
- [101] Ferguson SJ, Langhoff JD, Voelter K, von Rechenberg B, Scharnweber D, Bierbaum S, et al. Biomechanical comparison of different surface modifications for dental implants. *Int J Oral Maxillofac Implants* 2008;23:1037–46.
- [102] Kokkinos PA, Zarkadis IK, Kleitsas D, Deligianni DD. Effects of physiological mechanical strains on the release of growth factors and the expression of differentiation marker genes in human osteoblasts growing on Ti–6Al–4V. *J Biomed Mater Res A* 2009;90:387–95.
- [103] Huiskes R. The various stress patterns of press-fit, ingrown, and cemented femoral stems. *Clin Orthop* 1990;261:27–32.
- [104] Huiskes R, Weinans H, Dalstra M. Adaptive bone remodeling and biomechanical design considerations for noncemented total hip arthroplasty. *Orthopedics* 1989;12:1255–62.
- [105] Lewis JL, Askew MJ, Wixson RL, Kramer GM, Tarr RR. The influence of prosthetic stem stiffness and of calcar-collar contact stresses in the proximal end of the femur with a cemented femoral component. *J Bone Joint Surg* 1984;63A:280–6.
- [106] Bruck SD. Biostability of materials and implants. *Long Term Effect Med Implant* 1991;1:89–106.
- [107] Adell R, Lekholm U, Rockler B, Brånemark PI. A 15 year study of osseointegrated implant in the treatment of the edentulous jaw. *J Oral Surg* 1981;10:387–416.
- [108] Marchant RE. Cell attachment and interactions with biomaterials. *J Adhes* 1986;20:211–5.
- [109] Brunette DM. The effects of implant surface topography on the behavior of cells. *Int J Oral Maxillofac Implants* 1988;3:231–46.
- [110] Bigerle M, Anselme K, Noël B, Ruderman I, Hardouin P, Iost A. Improvement in the morphology of Ti-based surfaces: a new process to increase in vitro human osteoblast response. *Biomaterials* 2002;23:1563–77.
- [111] Nan H, Ping Y, Xuan C, Yongxang L, Xiaolan Z, Guangjun C, et al. Blood compatibility of amorphous titanium oxide films synthesized by ion beam enhanced deposition. *Biomaterials* 1998;19:771–6.
- [112] Stanford CM, Keller JC, Solursh M. Bone cell expression on titanium surfaces is altered by sterilization treatments. *J Dent Res* 1994;73:1061–71.
- [113] Carlsson LJ, Albrektsson A, Berman C. Bone response to plasma-cleaned titanium implants. *Int J Oral Maxillofac Implants* 1989;4:199–204.
- [114] Buser D, Schenk RK, Steinmann S, Fiorellini JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. *J Biomed Mater Res* 1991;25:889–902.
- [115] Knabe C, Klar F, Fitzner R, Radlanski RJ, Gross U. In vitro investigation of titanium and hydroxyapatite dental implant surfaces using a rat bone marrow stromal cell culture system. *Biomaterials* 2002;23:3235–45.

- [116] Baier RE. Modification of surfaces to meet bioadhesive design goals: a review. *J Adhes* 1986;20:171–86.
- [117] Glantz P-O, Baier RE. Recent studies on nonspecific aspects of intraoral adhesion. *J Adhes* 1986;20:227–44.
- [118] Sunny MC, Sharma CP. Titanium-protein interaction: change with oxide layer thickness. *J Biomater Appl* 1991;5:89–98.
- [119] Rahal MD, Delorme D, Brånemark P-I, Osmond DG. Myelointegration of titanium implants: B lymphopoiesis and hemopoietic cell proliferation in mouse bone marrow exposed to titanium implants. *Intl J Oral Maxillofac Implants* 2000;15:175–84.
- [120] Sukenik CN, Balachander N, Culp LA, Lewandowska K, Merritt K. Modulation of cell adhesion by modification of titanium surfaces with covalently attached self-assembled monolayers. *J Biomed Mater Res* 1990;24:1307–23.
- [121] Anselme K. Osteoblast adhesion on biomaterials. *Biomaterials* 2000;21:667–81.
- [122] Dmytryk JJ, Fox SC, Moriarty JD. The effects of scaling titanium implant surfaces with metal and plastic instruments on cell attachment. *J Periodontol* 1990;61:491–6.
- [123] Ryhänen J, Kallioinen M, Tuukkanen J, Lehenkari P, Junila J, Niemelä E, et al. Bone modeling and cell-attachment interface responses induced by nickel-titanium shape memory alloy after periosteal implantation. *Biomaterials* 1999;20:1309–17.
- [124] Larsson C, Thomsen P, Aronsson B-O, Rodahl M, Lausmaa J, Kasemo B, et al. Bone response to surface-modified titanium implants: studies on the early tissue response to machined and electropolished implants with different oxide thickness. *Biomaterials* 1996;17:605–16.
- [125] Larsson C, Thomsen P, Lausmaa J, Rodahl M, Kasemo B, Ericson LE. Bone response to surface modified titanium implants: studies on electropolished implants with different oxide thickness and morphology. *Biomaterials* 1994;15:1062–74.
- [126] de Oliveira PT, Nanci A. Nanotexturing of titanium-based surfaces upregulates expression of bone sialoprotein and osteopontin by cultured osteogenic cells. *Biomaterials* 2004;25:403–13.
- [127] Ahmad M, Gawronski D, Blum J, Goldberg J, Gronowicz G. Differential response of human osteoblast-like cells to commercially pure (cp) titanium grades 1 and 4. *J Biomed Mater Res* 1999;46:121–31.
- [128] Inoue T, Cox JE, Pilliar RM, Melcher AH. Effect of the surface geometry of smooth and porous-coated titanium alloy on the orientation of fibroblasts in vitro. *J Biomed Mater Res* 1987;21:107–26.
- [129] Anselme K, Linez P, Bigerelle M, Le Maguer D, Le Maguer A, Hardouin P, et al. The relative influence of the topography and chemistry of TiAl6V4 surfaces on osteoblastic cell behaviour. *Biomaterials* 2000;21:1567–77.
- [130] Mustafa K, Pan J, Wroblewski J, Leygraf C, Arvidson K. Electrochemical impedance spectroscopy and X-ray photoelectron spectroscopy analysis of titanium surfaces cultured with osteoblast-like cells derived from human mandibular bone. *J Biomed Mater Res* 2002;59:655–64.
- [131] Lee TM, Chang E, Yang CY. Attachment and proliferation of neonatal rat calvarial osteoblasts on Ti6Al4V: effect of surface chemistries of the alloy. *Biomaterials* 2004;25:23–32.
- [132] Zhu X, Chen J, Scheideler L, Reichl R, Geis-Gerstorfer J. Effects of topography and composition of titanium surface oxides on osteoblast responses. *Biomaterials* 2004;25:4087–103.
- [133] Hazan R, Brenner R, Oon U. Bone growth to metal implants is regulated by their surface chemical properties. *Biomaterials* 1993;14:570–4.

- [134] Jasty M, Bragdon CR, Haire T, Mulroy RO, Harris WH. Comparison of bone ingrowth into cobalt chrome sphere and titanium fiber mesh porous coated cementless canine acetabular components. *J Biomed Mater Res* 1993;27:639–44.
- [135] Simske SJ, Sachdeva R. Cranial bone apposition and ingrowth in a porous nickel–titanium implant. *J Biomed Mater Res* 1995;29:527–33.
- [136] Chang Y-S, Oka M, Kobayashi M, Gu H-O, Li Z-L, Nakamura T, et al. Significance of interstitial bone ingrowth under load-bearing conditions: a comparison between solid and porous implant materials. *Biomaterials* 1996;17:1141–8.
- [137] Li J, Liao H, Fartash B, Hermansson L. Surface-dimpled commercially pure titanium implant and bone ingrowth. *Biomaterials* 1997;18:691–5.
- [138] Kujala S, Ryhänen J, Jämsä T, Danilov A, Saaranenm J, Pramila A, et al. Bone modeling controlled by a nickel–titanium shape memory alloy intramedullary nail. *Biomaterials* 2002;23:2535–43.
- [139] Castleman LS, Motzkin SM, Alicandri FP, Bonawit VL. Biocompatibility of Nitinol alloy as an implant material. *J Biomed Mater Res* 1976;10:695–731.
- [140] Nishiguchi S, Nakamura T, Kobayashi M, Kim H-M, Miyaji F, Kokubo T. The effect of heat treatment on bone-bonding ability of alkali-treated titanium. *Biomaterials* 1999;20:491–500.
- [141] Villermaux F, Tabrizian M, Yahia L'H, Meunier M, Piron DL. Excimer laser treatment of NiTi shape memory alloy biomaterials. *Apply Surf Sci* 1997;109/110:62–6.
- [142] Montero-Ocampo C, Loprez H, Salinas Rodriguez A. Effect of compressive straining on corrosion resistance of a shape memory Ni–Ti alloy in ringer's solution. *J Biomed Mater Res* 1996;32:583–91.
- [143] Trépanier C, Tabrizian M, Yahia L'H, Bilodeu L, Piron DL. Effect of modification of oxide layer on NiTi stent corrosion resistance. *J Biomed Mater Res Appl Biomater* 1998;43:433–40.
- [144] Ku C-H, Browne M, Gregson PI, Corbeil J, Pioletti DP. Large-scale gene expression analysis of osteoblasts cultured on three different Ti–6Al–4V surface treatments. *Biomaterials* 2002;23:4193–202.
- [145] Piattelli A, Degidi M, Paolantonio M, Mangano C, Scarano A. Residual aluminum oxide on the surface of titanium implants has no effect on osseointegration. *Biomaterials* 2003;24:4081–9.
- [146] Meyer U, Joos U, Mythili J, Stamm T, Hohoff A, Fillies T, et al. Ultrastructural characterization of the implant/bone interface of immediately loaded dental implants. *Biomaterials* 2004;25:1959–67.
- [147] Kaneko S, Tsuru K, Hayakawa S, Takemoto S, Ohtsuki C, Ozaki T, et al. In vivo evaluation of bone-bonding of titanium metal chemically treated with a hydrogen peroxide solution containing tantalum chloride. *Biomaterials* 2001;22:875–81.
- [148] Gil FJ, Rodriguez A, Espinar E, Llamas JM, Padullés E, Juárez A. Effects of oral bacteria on the mechanical behavior of titanium dental implants. *Int J Oral Maxillofac Implants* 2012;27:64–8.
- [149] Chang JC, Oshida Y, Gregory RL, Andres CJ, Barco TM, Brown DT. Electrochemical study on microbiology-related corrosion of metallic dental materials. *Biomed Mater Eng* 2003;13:281–95.
- [150] Sarma B, Ravi Chandran KS. Recent advances in surface hardening of titanium. *J Met* 2011;63:85–92.
- [151] Marinucci L, Balloni S, Becchetti E, Belcastro S, Calvitti M, Lilli C, et al. Effect of titanium surface roughness on human osteoblast proliferation and gene expression in vitro. *Int J Oral Maxillofac Implants* 2006;21:719–25.

- [152] Chen X, Nouri A, Li Y, Lin J, Hodgson PD, Wen C. Effect of surface roughness of Ti, Zr, and TiZr on apatite precipitation from simulated body fluid. *Biotechnol Bioeng* 2008;101:378–87.
- [153] Singh RG. Evaluation of the bioactivity of titanium after varied surface treatments using human osteosarcoma osteoblast cells: an in vitro study. *Int J Oral Maxillofac Implants* 2011;26:998–1003.
- [154] Park JW, Jang JH, Lee CS, Hanawa T. Osteoconductivity of hydrophilic microstructured titanium implants with phosphate ion chemistry. *Acta Biomater* 2009;5:2311–21.

9 Other Applications

9.1 Introduction

The deterioration of hard tooth tissues, most often because of attrition and caries processes, makes normal functioning of stomatognathic systems very difficult. In the case of defects in hard tooth tissues, the defects are either filled or the damaged tooth is replaced with an implant. One of the popular methods applied in repairing human joints is endoprosthetics, that is, a surgical treatment consisting of replacing a diseased joint with an artificial apparatus—an endoprosthesis. Biomaterials used for these purposes, besides having a number of biofunctional features, should have very good tribological characteristics—low friction coefficients and antiwear performance. There are two types of implants: intraoral and extraoral implants. The former is used in a limited area inside the mouth for treating diseased tooth structure using implant and implant-supported prosthesis, while the latter refers to treatment of other areas of the human body for reconstruction of diseased and/or damaged body parts including eyes, noses, ears, maxillofacial area, hips, and all types of joints such as shoulders, elbows, fingers, knees, and ankles. These dental implants (intraoral implants), and orthopedic and otolaryngology or ENT (ear, nose, and throat) implants (extraoral implants) are discussed in Chapter 8. In this chapter, a variety of titanium applications other than the implants will be described. Some applications are realized owing to advanced and modified manufacturing technologies, and other applications are developed and promoted due to a material's uniqueness, such as superelasticity (SE) and/or shape memory effect (SME) associated with NiTi alloys.

9.2 Denture Bases

Denture materials are materials which require precise fabrication (or these prostheses should be manufactured in a near-net-shape form). Traditionally, various types of polymers have been used, including polymethylmethacrylate (PMMA), polycarbonate, polystyrene, and polysulfone. However, any polymeric resins have drawbacks. These include weakening of mechanical properties due to water sorption, which also causes a dimensional instability, and tissue irritation due to unavoidable residual unpolymerized monomer.

Commercially pure titanium (CpTi) and Ti-based alloys are generally used as fixtures for dental implantation [1,2]. When these metals are used as restoratives for anterior teeth, the metal prostheses are generally covered with esthetic materials, such as porcelain or resin. Veneering resin is more popular than porcelain because it is less expensive and more resistant to abrasion [3]. When constructing removable dentures, implant-supported prostheses, and most especially resin-bonded bridges, the interfacial bond between metal and acrylic resin has been wholly reliable or durable [4]. Numerous investigations have been carried out to measure metal/acrylic resin bond strengths between materials that have surface or chemical modifications that are reported to enhance retention [4–6]. These have included surface treatments of the alloys by macromechanical, micromechanical, and chemical methods, or by the addition of chemical bonding agents to the acrylic [6,7]. PMMA resins have a linear thermal coefficient of expansion of 81×10^{-6} m/m °C, whereas noble and base metals range from 7 to 19×10^{-6} m/m °C [8]. The lack of adhesion and differences in the thermal expansion of the materials places severe demands on the metal/acrylic resin surfaces. Ban [1] prepared CpTi (grade I), Ti–6Al–4V, experimental β -Ti alloy (54Ti–29Nb–13Ta–4.6Zr) and 12Au–20Pd–52Ag–15Cu–1Zn alloy plates which were sand blasted with alumina Al_2O_3 powder (100–250 μm), water washed, and dried. CpTi plates were further oxidized in air at 600°C for 1 h. They were also treated in 5 M LiOH, 5 M KOH, and 5 M NaOH at 25°C or 60°C for 20 h, followed by in-air oxidation at 600°C for 1 h. The bonding strengths of such treated CpTi plates were measured using a pull-shear bonding method after immersion in physiological saline solution at 37°C for 24 h. It was reported that (i) the bonding of the standard alkaline-treated CpTi and two Ti alloys to resin were 1.5–1.9 times stronger than those of sand-blasted specimens, but no significant effects of the alkaline treatment were observed on 12Au–20Pd–52Ag–15Cu–1Zn alloy, (ii) the greatest bonding strengths were found for CpTi treated with NaOH and KOH and then heated at 600°C, and (iii) alkaline treatment is a simple, effective surface modification of Ti that improves bonding to veneering resin [1].

The recognition that a chemical linkage between acrylic resin and metal would lead to an enhanced bond that led to the development and use of an intermediate layer based upon silicon oxide. The so-called “SiO–C” layer was introduced as an intermediate layer between the metal substrate and polymer as a means for enhancing the strength and durability of the bond [9]. Ti–6Al–4V, after bonding, was stored at 37°C in distilled water for 7 days followed by thermocycling between 5°C and 55°C for 500 cycles (for 21 days) and then was subjected to four-point bending at a crosshead speed of 0.5 mm/min. The bond strength $\sigma = F(L - \ell)/\pi R^3$, where σ is in N/m^2 , F is the load at failure (N), L is the distance between specimen support (m) = 0.024 m, ℓ is the distance between loading bars (m) = 0.008 m, and R is the radius of specimen (m) = 0.0035 m. It was concluded that the most durable surface treatment was the silicon-coating process after sand blasting of the metal surface with 250 μm alumina for heat-cured acrylic resin materials [10].

Denture bases are now mainly manufactured by a casting process of Co–Cr or Ni–Cr alloys. A novel superplastic fabrication process for dentures, as well as

implant systems, has been developed [11]. Ti–6Al–4V alloy is known as a bio-compatible metal, and with both high strength and low density, it seems to be the best material for denture bases. The Ti–6Al–4V also has superplastic properties at high temperature, forming by very simple processes by argon pressure (10 kg/cm^2) at $800\text{--}900^\circ\text{C}$. Superplastically formed (SPFed) denture bases of Ti–6Al–4V showed some merits compared with conventional cast or cold-pressed denture base plates, namely good fitness, light weight, and low production cost using a smaller number of manufacturing processes [12]. A SPFed Ti–6Al–4V removable denture framework was fabricated. Clinical application in short-term follow-up periods from 6 months to 3 years was evaluated. It was reported that (i) the dentures functioned well and did not cause any major clinical difficulties and (ii) the patients have expressed satisfaction with the dentures at regular recall appointments [13].

Srimaneepong et al. [14] had cast Ti–6Al–7Nb alloy into three differently designed, removable partial denture (RPD) frameworks: palatal strap, anterior–posterior bar, and horseshow-shaped bar. The vertical displacement and local strain of Ti–6Al–7Nb alloy frameworks were investigated to compare against those of Co–Cr alloy frameworks. A vertical loading force of 19.6 N was applied at two locations, 10 and 20 mm, from the distal end of the frameworks. It was found that (i) although higher vertical displacement and local strain were observed for Ti–6Al–7Nb alloy frameworks than those for Co–Cr alloy frameworks, the palatal strap framework appeared to show the least deformation, (ii) the strain at 10-mm location was higher than that at 20-mm location for anterior–posterior bar and horseshow-shaped frameworks, and (iii) the palatal strap design was evaluated to be a suitable design for the removable denture framework with Ti–6Al–7Nb alloy [14].

9.3 Crowns and Bridges, and Abutment

Zhang et al. [15], using a combination of wax patterns fabricated by a CAD/CAM system and a nonexpanded investment, investigated the casting accuracy. Three types of experimental magnesia-based investments were made and their properties were evaluated for dental use. Two kinds of wax patterns for full-coverage coping crowns were fabricated using a commercial CAD/CAM system. A traditional method using inlay wax was used for comparison purpose. The investment for titanium casting was decided from the fundamental data of experimental investment. Titanium crowns were replaced on the stone die and the thickness of the cement layer was evaluated. It was reported that (i) there were no significant differences for the setting time and setting expansion among the experimental investments, but the aluminous cement content played a role in hardening the mold, (ii) the fit of the titanium crowns differed significantly among the traditional method and the CAD/CAM system, and (iii) the range of thickness obtained from the traditional method was $20.78\text{--}357.88 \text{ }\mu\text{m}$, that for cement space of $0 \text{ }\mu\text{m}$ was $25.12\text{--}107.46 \text{ }\mu\text{m}$, and that for cement space of $20 \text{ }\mu\text{m}$ was $17.84\text{--}58.92 \text{ }\mu\text{m}$.

Dental porcelains provide dentistry with biologically acceptable and esthetic (tooth-colored restoration) methods of repairing diseased and fractured teeth [16]. Modern dental porcelains are pigmented glass-crystal composites that were evolved from traditional ternary whiteware compositions, namely clay–feldspar–quartz. Most of the modern dental porcelains used for the fabrication of crowns and bridges require only short, low-temperature sintering cycles. Porcelains have been fluxed so that their thermal expansions match precious or nonprecious alloys. Such alloys are manufactured into frameworks for the crowns or bridges, and the porcelains are bonded to them. The metal crown or bridge is faced or veneered with porcelain. The bond between precious alloys and the porcelain is more reliable than the bond between nonprecious alloys and the porcelain. The presence (by alloying in the original coping materials or coating on the coping materials) of small amounts of tin (Sn) or indium (In) in the precious coping alloys makes the chemical bonding possible in these cases. It is generally believed that oxygen in InO and SnO shares with oxygen in the silica component in porcelain, resulting in enhanced bonding strengths. All these porcelains have been opacified as to cover their dark metal-oxide background. They are highly reflective and are inferior esthetically for use in anterior teeth. Porcelains formulated for metal–ceramic prostheses have a tendency to densify during long and successive firing cycles [16].

PFM (porcelain-fused-to-metal) is sometimes called PBM (porcelain-bonded-to-metal), PTM (porcelain-to-metal), Ceramometal, or Metal–Ceramics. According to fusing temperature, porcelain can be classified into (1) high fusing (1300°C) for denture tooth fabrication, (2) medium fusing (1100–1300°C) for denture tooth fabrication, (3) low fusing (850–1100°C) for crown/bridge construction, and (4) ultralow fusing (<850°C) for crown/bridge construction. As for metallic coping materials, they are also classified into (1) high noble (Au–Pt–Pd, Au–Pd–Ag, Au–Pd), (2) noble (Pd–Au, Pd–Au–Ag, Pd–Ag, Pd–Cu, Pd–Co, Pd–Ga–Ag), and (3) base metal (CpTi, Ti–Al–V, Ni–Cr–Mo–Be, Ni–Cr–Mo, Co–Cr–Mo, Co–Cr–W).

There are several requirements and characteristics of metals applicable to the metal–ceramic systems as follows.

1. The metal should have a high melting point so that it does not melt during the porcelain application procedure.
2. The metal should have a similar coefficient of thermal expansion as those values in porcelain. The coefficients of thermal expansion (linear), α (in $\times 10^{-6}$ m/m °C, or simply in ppm), for major materials are reported as follows: conventional high-fusing porcelain (13.7–15.5 ppm), conventional low-fusing porcelain (14.1–15.1 ppm), low-fusing porcelain for Ti veneering (7.7–8.9 ppm), Au–Pd (13.9 ppm), high Pd (14.7 ppm), Ni–Cr base metal (13.9 ppm), CpTi (9.7 ppm) [16].¹

However, a slight extent of thermal mismatching is favored by $\alpha_{\text{METAL}} > \alpha_{\text{PORCELAIN}}$, so that the porcelain will be placed under the compression on cooling.

¹ When the volumetric expansion, γ , needs to be calculated, it follows as: $\gamma = 1 - (1 - \alpha)^3 = 1 - (1 - 3\alpha + 3\alpha^2 - \alpha^3) \approx 3\alpha$, since α^2 (in order of 10^{-12}) and α^3 (in order of 10^{-18}) are small enough to be neglected.

1. The metal should have excellent castability (however, casting is not only a fabrication method, but it should also include CAD/CAM or superplastic forming).
2. Both materials should have similar values of modulus of elasticity (MOE) to establish the mechanical compatibility [18].

Interface between coping material and porcelain has been characterized. Zinelis et al. [19], using SEM, backscattered electron imaging, and X-ray EDS analysis, characterized the interface and determined the bond strength of commercially available low-fusing dental porcelain to CpTi. Metal–ceramic specimens were tested in three-point bending at a crosshead speed of 1.5 mm/min according to ISO 9683 requirements. Interfacial characterization showed the mutual diffusion of Ti, Si, O, and La along Ti–ceramic interface. The results of bond strength classified the materials in the following decreasing order: TiKrom (paste) > Duceratin > Initial Ti > Duceratin Plus > Ti-22 > Triceram (paste) > Triceram (powder) > TitanKeramik. It was further reported that there is no correlation between the fracture mode and bond strength of the selected material, denoting that the fracture mode is irrelevant with the bond strength of Ti–ceramic joint; thus the former should be applied for comparison among different materials.

Although the following discussion is not directly relevant to the scope of this book, it is worth discussing the effects of crosshead speed on bonding strength. Oshida and Miyazaki [20], recognizing the evidence that there are certain values of crosshead speeds when dentin bond strengths are evaluated, further examined the effects of various crosshead speeds among numerous scattered articles on resulting dentin bond strengths. The results are summarized in Figure 9.1, where obtained dentin bond strengths (σ) are plotted against crosshead speed ($\dot{\epsilon}$) in a log–log plot. It was found that the dentin bond strength should be tested under the crosshead speed at or lower than 1.0 mm/min otherwise the resultant dentin bond strength can be manipulated by arbitrarily selected crosshead speed, because the strain rate sensitivity parameter, m , is not zero; in other words, the result is affected by selected/ conducted crosshead speed. Accordingly, when bond strengths are evaluated, the selection of appropriate level of crosshead speed becomes crucial.

The effects of thermal and mechanical cycling on ceramic bond strength to CpTi were investigated [21]. Metallic frameworks cast in gold alloy and CpTi were obtained and were subject to airborne particle abrasion with 150 μm alumina. Water storage was done at 37°C for 24 h. Thermal cycling was conducted for 3000 cycles between 4 and 55°C. Furthermore, mechanical cycling was performed for 20,000 cycles under 10 N load, immersion in distilled water at 37°C. It was reported that mechanical and thermal cycling decreased the flexural strength results significantly (29 MPa) compared to the control group (39 MPa). Similarly, Vázquez et al. [22] evaluated the effect of thermal- and mechanical cycling on the shear bond strength of three low-fusing glassy matrix dental ceramics to CpTi when compared to conventional feldspathic ceramic fused to gold alloy. Metallic frameworks were cast in CpTi and gold alloy, airborne particles abraded with 150 μm alumina. Low-fusing glassy matrix ceramics and a conventional feldspathic ceramics were fired onto the alloys. Four experimental groups were prepared: G1 (control group),

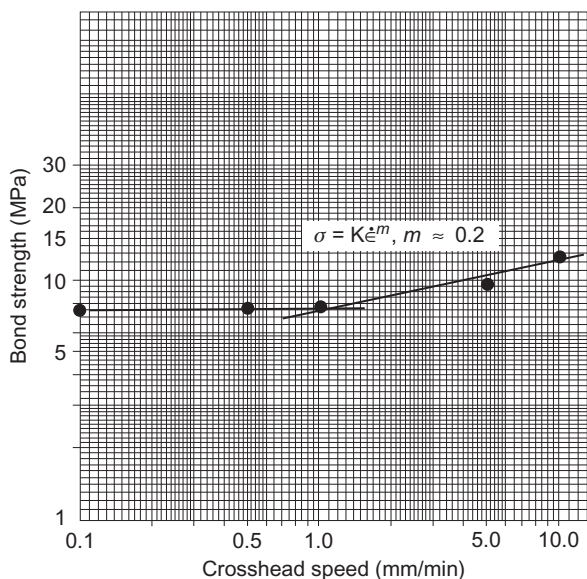


Figure 9.1 Crosshead speed dependency of dentin bond strengths.

G2: Triceram-CpTi, G3: Super Porcelain Ti22-CpTi, and G4: Vita Titankeramik-CpTi. While half of the specimens from each ceramic–metal combination were randomly tested without aging (water storage at 37°C for 24 h), the other half were first thermocycled (6000 cycles between 5°C and 55°C at the dwell time 13 s) and then mechanically loaded (20,000 cycles under 500 N load, immersion in distilled water at 37°C). The ceramic–alloy couples were loaded under shear at crosshead speed of 0.5 mm/min. It was found that (i) thermal- and mechanical cycling decreased the bond strength results significantly for G3 (33.4 MPa) and G4 (32 MPa) when compared to the nonaged groups (43 and 42 MPa, respectively) and (ii) G1 was not affected significantly by aging conditions (61 MPa for control and 61 MPa after aging).

Furthermore, Elsaka and Swain [23], studying the effects of different chemical surface treatments on porcelain–Ti, prepared 230 specimens of machined CpTi plates (grade II). These plates were differently treated in 10 ways: G1 (control, as-machined), G2 (sand blasted), G3 (CH₂Cl₂ for 5 min), G4 (CH₂Cl₂ for 10 min), G5 (10% H₂O₂ for 5 min), G6 (10% H₂O₂ for 10 min), G7 (30% H₂O₂ for 5 min), G8 (30% H₂O₂ for 10 min), G9 (9% HF for 5 min), and G10 (9% HF for min). It was reported that (i) groups treated with 9% HF or CH₂Cl₂ baths for 5 or 10 min showed the highest adhesion values (ranging from 23 to 34 J/m²) and (ii) the machined group demonstrated the lowest value (8 J/m²) [23].

Moreover, since little or no residual stress due to thermal mismatch should exist in the final Ti/porcelain bond interface, the significant discrepancies already noted in their thermal coefficients of expansion will have to be modified to match more closely. It appears that an interfacial oxide layer, some 100–1000 nm (10–100 Å)

thick, forms during firing, and the thicker this layer becomes, the weaker the bonding strength between the porcelain and the titanium [24].

To have a reasonable function of Ti/porcelain system, the rigid bonding is crucial in terms of in-service longevity. There are several theories to postulate the bonding mechanism of porcelain.

1. *Chemical bonding.* A chemical bonding, existing through the formation of a tin (or indium) oxide layer during porcelain firing and that the oxide formed provides the mechanism of bonding between the porcelain and the metal substrate. Watanabe et al. [25] characterized the interface reaction between porcelain and pure titanium during porcelain firing, using an electron probe microanalyzer (EPMA), X-ray diffraction method, and Fourier transform infrared spectroscopy. It was reported that (i) separation occurred partly at the interface between titanium and porcelain and partly slightly inside the porcelain after firing three times at 760°C, (ii) in the surface layer of the titanium side, only oxygen was detected as a diffusing element, (iii) X-ray diffraction indicated a decrease in SnO₂ and revealed β -Sn (metallic Sn), and (iv) a considerable amount of TiO₂ was formed at the interface when fired at 760°C for 2 min [26].
2. *Mechanical retention through various surface modifications.* Although chemical bonding is generally regarded to be responsible for metal–porcelain adherence, evidence exists that mechanical interlocking provides the principal bonding. Surface concave texturing (resulting in remarkable increase in an effective surface area) will enhance the porcelain bond strength. While potential contamination of sand blasting and shot peening media (mostly 50 μ m alumina powder) weakens the porcelain bond strength, different techniques recently produced similar effects, such as a contamination-free indirect laser peening, and chemical treatment (in either acid or alkaline).
3. *Compressive forces.* In order to strengthen the fused porcelain body (in other words, to retard the crack propagation), there are three major methods available: (i) thermal tempering by rapid cooling the surface of the objects while it is hot and in its molten state, (ii) ion exchange by substituting small ion (e.g., Na) with a larger ion (e.g., K), and (iii) thermal mismatching by $\alpha_{\text{METAL}} > \alpha_{\text{PORCELAIN}}$, where the porcelain will be placed under the compression on cooling.
4. *Bonding agent application.* In order to enhance the bond strength or improve the wettability of porcelain, a bonding agent or metal conditioner is applied. In some cases, hydrofluoric acid (HF) treatment is recommended to remove silicate from the investing materials.
5. *Physical bonding.* X-ray microanalysis on CpTi/porcelain and Ti–6Al–7Nb/porcelain gave some evidence of diffusion of some elements, particularly of the porcelain into the metal, which may assist bonding during firing [26]. Diffusion of elements in porcelain into the titanium (i.e., titanium oxide) during the firing process is also significant in porcelain-fused-to-titanium systems because bonding occurs between the two components by the mutual diffusion of elements. Hanawa et al. [27] investigated the diffusion of elements of commercial porcelain for titanium into titanium oxide during heating. Titanium was deposited on three kinds of disk-shaped porcelains by vacuum vaporization and the porcelains were then heated. A thin titanium oxide film was formed on the porcelains by the heating. X-ray photoelectron spectroscopy (XPS) was used to characterize the surfaces of the porcelain with and without titanium oxide. It was found that (i) only sodium, potassium, and barium diffused into titanium oxide during heating, where they formed a complex oxide with titanium, (ii) the diffusion of these elements may be involved in the bonding of porcelain to titanium, and (iii) after heating, the titanium oxide layer mainly

consisted of a titanium oxide, whose valence was between trivalent and tetravalent, and contained small amounts of sodium, potassium, and barium [27].

If titanium's distinct advantages (such as light weight, high strength, good corrosion resistance) are to be used for esthetic crowns and bridges, the ability to apply a porcelain veneer becomes important. Because of titanium's high affinity for oxygen, porcelain firing should take place below 800°C (which is below the 885°C $\alpha \leftrightarrow \beta$ transformation temperature) in order to prevent excess oxide formation [24,28]. There are two major problems in the Ti/porcelain system, as mentioned above. The first one is related to the coefficient of thermal expansion. The coefficient of thermal expansion of titanium is not same as that of porcelain. Hence, this requires the development of a new titanium material which has an equivalent thermal coefficient value. Alternatively, a new porcelain system must be developed to exhibit the thermal compatibility. The second concern deals with the rapid oxidation of titanium. The conventional firing temperature is in a range 700–800°C, at which the titanium substrate will be easily oxidized to form a relatively thick oxide film, causing a weakening of the bond strength. As mentioned above, it is obvious that the heating temperature should not exceed the β -transus temperature (i.e., 885°C for pure titanium), since the oxidation rate will accelerate if the process temperature is above the β -transus. Besides, there are differences in physical properties between the α -phase (low-temperature HCP structure) and the β -phase (high-temperature BCC structure), including lattice constants and thermal expansion coefficients. Therefore, several low-firing porcelain systems have been developed (including Procera porcelain, Vita Titanium Porcelain, Duceratin, Noritake Super Porcelain Titan, and Ohara Titan Bond). Alternatively, the porcelain firing process should be operated under a high vacuum condition or an argon-gas atmosphere.

Various casting processes have been developed for titanium in dentistry, some of which are used commercially. From the success of these casting procedures, the bonding of porcelain to titanium has been attempted, and several porcelains for titanium are now available commercially [27]. The bonding strength is primarily governed by a reaction layer existing between porcelain and titanium that is formed by the mutual diffusion of elements. In this regard, porcelain-fused-to-titanium systems have been studied. Togaya et al. [29] investigated the feasibility of using titanium in a metal–porcelain system and demonstrated properties of titanium at high temperatures. Adachi et al. [30] reported the relationship between the oxidation of titanium and Ti–6Al–4V and bonding strength; bonding strength is low when the thickness of the oxide layer reaches 1 μm . Kimura et al. [31] also examined the effects of oxidation on porcelain–titanium interface reactions and bonding strength and found a layer at the interface that is formed by the diffusion of titanium into the porcelain. Nagayama et al. [32] characterized the interface between titanium and porcelain using EPMA and XPS, and revealed that titanium atoms diffused into the porcelain and that a reaction layer was formed, possibly corresponding to that found by Kimura et al. [31]. During the interdiffusion process, a reaction layer between two bodies normally forms due to the fact that titanium atoms apparently diffuse into the porcelain during the firing process because only CpTi is used in porcelain-fused-to-

titanium systems at present. The three studies described above [29–31] show that titanium is easily oxidized during the firing process. In a porcelain-fused-to-titanium system, Oshida et al. [33,34] examined the oxidation kinetics of titanium during the porcelain firing process. Historically, there have been several attempts and ideas proposed to improve the porcelain bond strengths. Such modifications should include bonding agents improvements [35–37], titanium substrate modification (such as nitritization) to prevent excess oxidation during the firing process [33,34], sand blasting [38] or chemical texturing CpTi surface [39], firing process alternation in argon process [40], and improving the porcelain materials [41,42] (see also Chapter 11). To improve the bonding strength between Ti substrate and fired porcelain, a bonding agent is sometimes applied [27]. Bonding porcelain to titanium and its alloys is problematic if titanium is exposed to temperatures greater than 800°C, causing the formation of thick titanium oxide (TiO₂) layers. At approximately 1 μm thickness, the oxide layer will spontaneously delaminate from the surface due to the induced stresses caused by the volume differences between titanium and its oxides. While the use of fusing temperatures below 800°C have been found to increase porcelain-to-titanium bond strength, it does not eliminate the oxidation process. During firing, oxygen diffusing from the atmosphere and oxygen obtained from the reduction of porcelain oxides continue to react with titanium. A recently introduced bonding agent and low-fusing porcelain/titanium system is claimed by Nobelpharma to overcome these technical difficulties and provide adequate porcelain-to-metal bonding. A bonding agent that prepares the surface of milled titanium copings (by CAD/CAM machining for special cases) for bonding to low-fusing dental porcelains has recently been introduced. Gilbert et al. [35] evaluated the effectiveness of the bonding agent by comparing the shear and three-point bending strengths of specimens made with three combinations of materials: milled titanium/porcelain with bonding agent, the same milled titanium/porcelain without bonding agent, and cast high palladium/conventional porcelain. It was found that (i) when a titanium bonding agent was used, porcelain to titanium bond strength was found to be greater than the porcelain to high palladium bond strength in both a shear test (28.3 MPa) and a three-point bend test (300 MPa) and (ii) without the bonding agent, the shear strength (18.7 MPa) of porcelain to titanium was significantly decreased. Based on these findings, it was therefore concluded that (i) the elimination of the bonding agent application resulted in a significant decrease in the bond strength of porcelain to titanium as measured by the shear test but showed no significant effect in the flexure tests and (ii) sand blasting the titanium metal surfaces resulted in a significant amount of alumina becoming embedded in the titanium surface [35]. We will discuss the contamination issue in more detail in Chapter 11.

There is a concern with evaluation methods of bond strength of fired porcelain. It is known that a three-point bending test produces internal shear stress which does not exist between the two central loading points in a four-point bending test [43]. In Ti–porcelain systems, under the three-point bending conditions, there are at least two possible fracture processes: (1) a cohesive fracture (from external maximum-tensile side toward the interfacial zone) within a porcelain body, followed by

debonding the porcelain from titanium substrate and (2) delamination of porcelain from the titanium substrate, then followed by the cohesive fracture of the porcelain body. When a thin plate of double-layered structure is subjected to the three-point flexure tests, unlike the monolayer case, the central (neutral) axis may not necessarily be on the geometrical center line of the beam. It is located rather far from the geometrical center line due to a large difference in values of MOE between CpTi and the used porcelain.

The distance from the top of the beam to the neutral axis, c , can be calculated by; $c = \{[(E_2/E_1) h (h + 2t)] + t^2\} / \{2[(E_2/E_1) h + t]\}$, where E_2 is the MOE of porcelain, E_1 is the MOE of CpTi, h is a layer thickness of fired porcelain, and t is a layer thickness of CpTi substrate [44,45]. White et al. [44] conducted a three-point flexural test on porcelain–titanium system. The strength of layered porcelain–ceramic beams was limited by the cohesive tensile or compressive strengths of the porcelain, not by the porcelain–titanium interfacial bond, namely, the porcelain failure occurred at lower loads than did failure of the porcelain–titanium interface. It was reported that (i) the porcelain–titanium bond strength was at least 26 MPa and (ii) SEM and energy-dispersive X-ray spectroscopy demonstrated that the bond was limited by delamination of a thin Ti–Ti oxide interface. It was, therefore, suggested that from curves of relative layer and total thickness versus force-bearing capacity of model beam, porcelain–titanium prostheses should be made as thick as is practical, but that the relative thickness of the porcelain and titanium layers would be less important [44]. The Ti–porcelain system can be considered as a double-layer structure, composed of at least titanium substrate and porcelain body, including a bonding agent. The stress distribution patterns of such a double-layer structure are not necessarily the same as that of a single beam under the three-point bending testing mode. Previously tested porcelain-fired CpTi samples ($n = 285$) [34,39] were reevaluated. It was found that all higher maximum bond strength data were in an area where $c > t$, or, in other words, that the calculated neutral axis is located within the porcelain layer (actually in the bonding agent layer), while lower bond strengths were found when $c < t$ [46]. These results support conclusions by White et al. [44].

In contrast with most dental alloys for metal–ceramic restorations, titanium cannot be veneered with conventional feldspathic dental porcelains for several reasons [17]. As discussed above, at temperatures above 800°C, which are required for firing conventional dental porcelains (about 950°C), titanium oxidizes rapidly, producing a thick oxide layer with a rather weak bond to the underlying titanium, resulting in inadequate metal–ceramic bond strength [30,31]. Although low-fusing dental porcelains (firing temperature <800°C) are available for veneering dental alloys, the use of these porcelains on titanium substrates is limited owing to the great mismatch in the coefficients of thermal expansion, since CpTi (grades 1–4) has a much smaller thermal expansion coefficient (in units of 10^{-6} m/m °C, or ppm) than does conventional porcelain. Zinelis et al. [17] studied various Ti-based alloys with CpTi as a control. The tested Ti materials included Ti–18Sn, Ti–12Ga, Ti–18In, Ti–12Co and combinations of Ga + Sn, Co + Ga, In + Al,

and Sn + Al as alloying mixtures. It was reported that the addition of Al, Ga, In, Sn, Co, and Mg increased the coefficient of Ti to 10.1–13.1 ppm (25–500°C).

Eriksson et al. [47] employed a powder metallurgy-forming process to fabricate titanium copings. Titanium powder was pressed at 300–900 MPa, milled to the right shape, and sintered at 1200°C for a 2-h holding time. It was reported that the titanium in the sintered copings was ductile, dense (97% to 99% +), and free from open porosity after sintering, suggesting that the fabrication of copings with this sintering method could have a potential for becoming a very cost-efficient method of producing dental crowns.

Recently, several researches were conducted and reported about various surface modifications on titanium substrate for enhancing the porcelain bond strengths [48–51]. Troia et al. [48] treated CpTi surfaces with various chemicals including HF, NaOH, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, HCl, NaOH, HNO_3 , and these chemicals were mixed under various percentages and combinations. It was concluded that (i) the best combination surface treatment was NaOH 50% + $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 10% and (ii) fractographic observation revealed that a combination of cohesive and adhesive² fractures in NaOH + HNO_3 -treated substrate surfaces. Papadopoulos et al. [49], studying effects of ceramic coating on porcelain bond strength to CpTi substrate, had treated 72 patterns with a ceramic and invested with phosphate-bonded material (GA), and another 72 with magnesia material (GB), all cast with CpTi. It was reported that (i) modulus elasticity, E , of GA and GB were 98.3 and 98.6 GPa, respectively, (ii) the bond strength was 26 MPa (Ducoratin), 28 MPa (Noritake Ti22), 27 MPa (Triceram) for GA, and 24 MPa (Ducoratin), 28 MPa (Noritake), and 27 MPa (Triceram) for GB, and (iii) the mode of failure was mainly adhesive for all specimens. The influence of SiO_2 and $\text{SiO}_2\text{--TiO}_2$ was investigated on the bond strength of CpTi as well as Ti–6Al–4V alloy [50]. It was reported that (i) statistically significant higher bond strength of the metal–porcelain for Ti–6Al–4V (28 MPa), Ti–6Al–4V/ SiO_2 (32 MPa), and Ti–6Al–4V/ $\text{SiO}_2\text{--TiO}_2$ (36 MPa) was noted in comparison to CpTi substrates (23, 27, and 28 MPa), (ii) the nature of metal–intermediate coating porcelain bonding was both mechanical and chemical, and (iii) the failure was cohesive and adhesive, mainly adhesive. Elaska et al. [51], investigating the effects of chromium interlayer on the shear strength of porcelain to CpTi substrate, reported that (i) bond strength values were significantly affected by the type of Cr electroplating treatment (5% w/v of chromium nitrate solution, 10% w/v chromium nitrate solution) but not by the type of porcelain (Vita Titankeramik and Triceram) and (ii) the CpTi/Vita Titankeramik (treated under 10% for 0.5 h) and CpTi/Triceram (5% for 0.5 hr) showed the highest bond strengths (27 and 25 MPa).

² One can define the “bonding coefficient, η_α ” as ratio of bonding strength to the strength of the bonding agent itself. If σ_j and σ_α are tensile bonding strength and tensile strength of the bonding agent; while τ_j and τ_α are those for shear strengths, the tensile bonding coefficient, $\eta_{\alpha\sigma}$ and $\eta_{\alpha\tau}$ can be expressed by $\eta_{\alpha\sigma} = \sigma_j/\sigma_\alpha \times 100(\%)$ and $\eta_{\alpha\tau} = \tau_j/\tau_\alpha \times 100(\%)$. Hence, when the cohesive fracture takes place, both of the above bonding coefficients should be 100%, which is an ideal case.

Furthermore, there are several recent research works on abutments [52–56]. The study was carried out to assess the precision at the implant interface of titanium, zirconia, and alumina Procera abutments with a hexagonal connection for single-tooth restoration [55]. Twenty Procera abutments were produced with CpTi, 20 with zirconia, and 20 with alumina using computer-assisted design and manufacture (CAD/CAM). The rotational freedom of the abutments was assessed to detect the precision of fit of each abutment on top of the implant hexagon. It was reported that (i) significant differences relative to rotational freedom were found between groups; the titanium group and the zirconia group did not differ significantly but both demonstrated smaller mean rotational freedom than the alumina group, (ii) rotational freedom was less than three degrees for all abutments, and (iii) the hexagonal misfit of the Procera abutment on the implant hexagon may be implicated in screw joint loosening [52]. Vigolo et al. [53] further conducted a similar research project to assess the precision at the implant interface of gold-machined UCLA-type abutments and CAD/CAM titanium abutments with both external- and internal-hexagonal connection. It was reported that both types of abutments (gold-machined UCLA-type and CAD/CAM titanium) consistently showed one degree of rotational freedom between the implant and abutment in both cases of external- and internal-hexagonal connection. Ebert et al. [54] had evaluated the effects of two surface conditioning methods and to luting-gap sizes on the retention and durability of zirconia ceramic coping bonded to titanium abutments. Zirconia ceramic copings (Camlog Biotechnologies) with a luting-gap size of either 30 or 60 μm were bonded to titanium abutments using the composite resin cement Panavia F. The bonding surfaces of the zirconia ceramic coping were either (1) pretreated with airborne particle abrasion and cleaned with alcohol or (2) just cleaned with alcohol, whereas the bonding surfaces of all titanium abutments had been abraded and cleaned. After the specimens had been stressed for either 1, 30, 60, or 150 days by water and thermal cycling, retention strengths were measured. It was concluded that surface conditioning methods and the size of the luting gap had a significant influence on the retention of Camlog zirconia ceramic copings bonded to Camlog titanium abutments. The microgap between different zirconia abutments and their titanium implants was evaluated *in vivo* [55]. Four systems were evaluated: Procera zirconia, Cercon Balance Anterior, ZirDesign, and Straumanns Cares ceramic. It was reported that (i) the mean microgap observed for all tested systems was less than 2 μm , (ii) for each system, the microgap decreased quickly from the outer region to the inner region, and (iii) the mean gap was larger for flat-to-flat connection systems, compared to internal-connection systems with a conical interface. It was also mentioned that the precise fit of these abutments could lead to better biological and biomechanical behavior. Klotz et al. [56] employed the clinical simulation to determine whether wear of the internal surface of a titanium implant was greater following connection and loading of a one-piece zirconia implant abutment or a titanium implant abutment. Two implants received zirconia abutments and two received titanium abutments. The implants were secured into four fiber-reinforced epoxy resin disks that had been prepared to receive the internally connected implants. These couples were cyclically loaded off-axis for a total of 1,000,000 cycles. It was concluded that (i) the implants

with the zirconia abutments showed a greater initial rate of wear and more total wear than the implants with titanium abutments following cyclic loading and (ii) the amount of titanium transfer seen to zirconia abutment increased [56].

9.4 Clasps

RPD retentive clasp arms must be capable of placing and returning to original form and should satisfactorily retain a prosthesis [57]. In addition, clasps should not unduly stress abutment teeth or be permanently distorted during service. In this respect, gold alloys have been favored as clasps compared with base metal alloys because of high yield strengths and low moduli of elasticity [58]. However, gold alloys have not been regarded as the ideal metal for clasp construction due to the relatively high cost and unavoidable permanent deformation after long-term service. On the other hand, if clasps are too flexible, they may not provide adequate RPD retention when placed in shallow retentive undercuts. Accordingly, materials available to meet such requirements are limited. Co–Cr alloy, type IV gold alloy, and NiTi alloy are normally employed. NiTi clasps were made to engage one of the two retentive undercut depths. The force required to remove the clasps was measured using a universal testing machine with a crosshead speed of 10 mm/min. It was concluded that (i) the retentive force of all tested clasps, except NiTi alloy clasps, significantly decreased during cycling sequences simulating clasp placement and removal for 500 times, (ii) the end-point retention for all clasps was nearly identical, and (iii) NiTi alloy clasps might be suitable for removable prosthodontic restorations because the loss of retention during simulated service was significantly lower than losses recorded for other clasp materials studied [57].

Vallittu and Kokkonen [59] determined the fatigue resistance of the cast clasps of RPDs using Co–Cr, CpTi, Ti–6Al–4V, and gold alloy. The test method used was a constant-deflection fatigue test in which the force required to deflect the clasp for 0.6 mm and the number of loading cycles required to fracture the clasp were determined. The results revealed that a fatigue fracture occurred in the 63Co–29Cr–5Mo alloy clasp after about 25,000 cycles, in CpTi after 4500 cycles, in Ti–6Al–4V after 20,000 cycles, and the 72Au–3Pt–11Ag–13Cu alloy clasp 21,000 cycles. It was then suggested that significant differences exist in the fatigue resistance of removable denture clasps made from different commercial metals, which may cause the loss of retention of the RPD and clasp failures [59].

9.5 Posts and Cores

Restorations through post crowns have revolutionized the treatment of badly damaged teeth to be made functional over the past century. Posts and cores are often inserted in endodontically treated teeth to provide retention and stability for a crown or a fixed partial denture [60]. Posts are normally available for either a

prefabricated and retained-type post (actively or passively) or a custom made-type post. Posts are an essential component of the armamentarium involved with the retention of crowns and bridges. A standard post is cast gold with a zinc phosphate cement. Failure of the post, usually by loosening, will lead to catastrophic failure of the crowns and bridges. Concerns about possible toxic effects of the metals used in posts and the adverse stress concentration due to the mismatch in physical properties between the post, luting cement, and tooth have lead to the development of ceramic and composite posts using a variety of filler reinforcements with carbon and quartz fibers [61]. Among a number of factors influencing the long-term clinical performance of prefabricated posts and cores, retention of the core material is one of the most significant of these [62–68]. Most *in vitro* studies have been performed to evaluate the posts and cores subjected to tensile [69,70], compressive [70,71], and shear forces [72–74] as well as trauma and fatigue tests [75]. Clinically, however, posts are also subjected to torsional or rotational forces produced by functional tooth contacts [76,77]. Failures of posts and cores usually have serious consequences. Reasons for failure are loss of retention, with risk of caries development in the root canal and fracture of the root, the post, or the core. Some of these failures are related to the diameter, length, and mechanical properties—such as stiffness and flexural strength—of the post. Loss of retention of posts has been found to be the most frequent mode of failure, while root fracture is the most serious type of failure [78–82].

Akışli et al. [62] evaluated eight different core materials. Silica coating/silanization and acrylization were treated on CpTi posts. Following thermocycling ($5 \leftrightarrow 55^{\circ}\text{C}$, dwell time of 30 s, for 5000 cycles), maximum torsional forces were determined with an electronic torque movement key. It was reported that (i) the resistance to torsional forces for the core materials on Ti posts increased with the use of chemical surface conditioning techniques and varied in accordance with the opaque type, and (ii) the type of core materials also significantly influenced the resistance after thermocycling [62]. Kozono et al. [83] examined CpTi prefabricated post and its compatibility with cast metal core in comparison with those of the commercially available prefabricated posts made of Ni–Cr alloy and 304 (18Cr–8Ni–Fe) stainless steel. It was found that, although Ni–Cr and 304 stainless steel alloys were subjected to annealing during the casting process of the core, showing marked decrease in hardness and tensile strength, the CpTi post had already annealed during the working process and showed no significant changes in properties when heat treated up to 1000°C [83].

Schmage et al. [84] examined the metal surface conditioning on retention of composite resins to metal. The effect on tensile bond strength of (1) air-particle abrasion ($50\text{ }\mu\text{m Al}_2\text{O}_3$) and (2) silica coating ($30\text{ }\mu\text{m SiO}_2$) and silanization of tapered titanium posts prior to luting was evaluated. Following endodontic preparation of 100 intact anterior human teeth with hand instruments, the post spaces were prepared using the opening drills of the corresponding size of the posts. All posts were cemented into the roots. The specimens were first stored in water at 37°C for 24 h and then subjected to thermocycling (5000 cycles between 5°C and 55°C with dwell time of 30 s). The tensile strength was obtained with a universal testing

machine at a crosshead speed of 0.5 mm/min. It was concluded that (i) the composite resin luting cements did not show significant differences showing values between 352 and 475 N when the posts were air abraded and (ii) after silica coating and silanization, significantly higher tensile strengths (600 N) with Compolute Aplicap than those of the other luting cements (Flexi-Flow cemTM, Panavia 21 EX, Twinlook) [84].

9.6 Titanium Fiber and Oxide Powder as Reinforcement for Bone Cement

PMMA bone cement is used for maintaining the fixation of artificial joint components and for transferring loads from the artificial joint to the bone [85]. For artificial hips or knee, the bone cement must survive in a fatigue loading environment, and gross *in vivo* failure of bone cement occurs predominantly by fatigue fracture [86–89]. Even when the cause of loosening or failure of an artificial joint cannot be linked to obvious bone cement fracture, undetected fatigue microcracking can reduce the mechanical integrity of the PMMA, affect the load transfer capabilities, and alter the stress distributions within the prosthesis [90]. Methods to increase the *in vivo* fatigue life of currently used PMMA-based bone cements include improved surgical cementing techniques, porosity reduction by centrifugation or vacuum mixing and fracture resisting or toughening additives. One of the problems encountered in previous attempts to create an effective fiber-reinforced bone cement, for example, was that the cement viscosity increased with the addition of fibers, and mixing and delivery were difficult. Oshida and coworkers [91–93] investigated the best type of additives (ZrO_2 , TiO_2 , Al_2O_3 , MgO , CaO , and their mixture) as well as additive percentage to enhance mechanical properties of PMMA cement. It was found that adding titania alone or a mixture with zirconia (up to 1 vol%) to conventional bone cement polymeric material (PMMA cement) enhanced the mechanical strengths as well as fracture strength. Such enhancement was mainly due to crack branching strengthening mechanisms.

9.7 Sealer Material

It is noticed that zinc is considered as an allergic element. Hence, a new type of zinc-free sealer material for root canal treatments has been developed. The new type is a titanium oxide system sealer and satisfies ISO 6876 specifications [94]. The following applications are mainly realized using NiTi's physical and mechanical uniqueness—SME and SE. By SME, a material first undergoes a martensitic transformation. After deformation in the martensitic condition, the apparently permanent strain is recovered when the specimen is heated to cause the reverse martensitic transformation. Upon cooling, it does not return to its deformed shape. When SME alloys are deformed in the temperature regime a little above the

temperature at which martensite normally forms during cooling, a stress-induced martensite is formed. This martensite disappears when the stress is released, giving rise to a superelastic stress–strain loop with some stress hysteresis; this is the other unique property associated with NiTi—SE. There is a term called psuedoelasticity, which is a more generic term that encompasses both superelastic and rubberlike behavior. The following is a short list of important functions of NiTi medical devices [95,96]: (1) biomechanical compatibility, (2) thermal deployment (SME), (3) elastic deployment (SE), (4) hysteresis/biased stiffness, (5) kink resistance, (6) constancy of stress/temperature dependency, (7) fatigue resistance, (8) dynamic interference, (9) magnetic resonance compatibility, and (10) biocompatibility.

9.8 Shape Memory Effect Dental Implant

Fukuyo et al. [97] successfully introduced dental implant systems of perioroot type, as well as blade type, using NiTi shape memory alloy. It was reported that (i) the perioroot implant demonstrated excellent biocompatibility and provided for rigid and sustained bone compression in order to encourage bone adhesion and (ii) this implant system had the potential to be used in craniofacial surgery and other allied medical fields. Shape memory NiTi alloy has also been successfully utilized in an open blade-type dental endosseous implant to enhance the fixation force and to exhibit a strong ability of mastication compared with ordinary nonopening blade–type implants.

9.9 Orthodontic Appliances

For orthodontic applications, wires and brackets can be easily named. Between them, research and developments on wires are dominant over those involved with brackets. NiTi has a unique property which is of practical use to the orthodontist. That property is its extreme elasticity when it is drawn into high-strength wire. NiTi wire is much more difficult to deform during handling and seating in bracket slots than stainless steel wire. The wire can be used for longer periods of time without changing it, and it can shorten treatment time needed in leveling the dentition, due to its extreme elasticity [98]. Yoneyama et al. [99] investigated the effect of heat treatment temperature on bending properties and transformation temperatures of a SE NiTi alloy wire. The heat treatment process was at 440°C for 1800 s and between 400°C and 540°C for 1800 s. A three-point bending test and differential scanning calorimetry were performed. It was found that (i) the transformation temperatures of the wires were lowered with increasing the heat treatment temperature, (ii) the reverse transformation finishing temperature was below the body temperature with the treatment above 480°C, (iii) residual deflection of the NiTi wire after bending was small with the secondary heat treatment above 460°C, and (iv) the load in the unloading process was less changeable and increased with the

treatment temperature between 460°C and 540°C. Hence, it was concluded that secondary heat treatment in this range was suitable for using SE in expansion arch appliances [99].

There is evidence that orthodontic archwires can be recycled and reused among different patients [100]. Special attention should be placed on this practice because chemical degradation and mechanical damage of the archwire can accumulate as the frequency of recycling increases [101,102]. It is likely that nickel release from the NiTi might be accelerated, and some individuals may be sensitized to this reaction or may develop a hypersensitivity reaction. Furthermore, nickel-induced toxicity and carcinogenicity is well documented in the literature [103–105]. It has been reported that the rate of nickel allergy is increasing rapidly in the Western world [102]. Based on this background, Oshida et al. [106] microanalyzed orthodontic SE NiTi archwires of both used (4 weeks) and unused conditions. They were subjected to immersion and polarization corrosion tests in 0.9% NaCl solution. Based on the results, surfaces of NiTi archwires were further electrochemically treated to etch away Ni selectively and reform the surface morphology to uniform and porous surface layers. It was concluded that (i) surface layers of used wires were covered contaminants causing the discoloration, and the contaminants were identified as mainly KCl crystals, (ii) surfaces of both used and unused wires were observed to have irregular features characterized by lengthy island-like structures, where Ni was selectively dissolved, (iii) corrosion tests in 0.9% NaCl solution immersion and polarization methods indicated that by increasing temperature from 3°C to 60°C and acidity from pH 11 to 3, calculated corrosion rates increased, and (iv) surface layers of NiTi wires can be electrochemically modified to selectively etch Ni away, leaving a Ti-enriched surface layer and forming a uniformly distributed porous surface that may reduce the coefficient of friction against the orthodontic brackets [106].

Physio-mechanical properties of NiTi wire materials were investigated by Kusy and Wilson [107]. Tested materials were eight straight-wire materials, including four stable alloys: one TiMo (beta phase), three NiTi (martensite phase), and four active alloys: NiTi (martensite phase), NiTi (austenite phase), NiTi (biphase), and NiTi (hybrid martensite phase). With a tensile mode, each sample was scanned from -120°C to 200°C at $2^{\circ}\text{C}/\text{min}$. From the data, plots of log storage modulus, log tan delta, and percent change in length versus temperature were generated. It was shown that (i) the dynamic mechanical properties of the alloy within this Ti system are quite different, (ii) the TiMo alloy was invariant with temperature, having a modulus of $7.30 \times 10^{11} \text{ dyne}/\text{cm}^2$, and (iii) the three cold-worked alloys appeared to be similar, with 5.74×10^{11} [107].

Yanaru et al. [108] investigated the orthodontic forces of NiTi wires under the retained condition on the dental arch model and evaluated with the changes in temperature and deflection. The tested specimens were a commercially available SE NiTi wire and two SME NiTi wires with their nominal A_f (austenitic transformation finish) points were 35°C and 40°C . It was shown that (i) typical SE hysteresis loops under the restraint condition was at 40°C , (ii) the recovery forces in the plateau region at 1.0 mm deflection were much larger than desired in the clinical guidelines

around oral temperatures, and (iii) in the SME wire with A_f of 40°C, the recovery force rapidly decreased to zero by a small reduction of the deflection from its maximum, whereas the wire exerted the force with the remaining permanent deflection by raising temperatures [108].

Kwon et al. [109] examined extensively the effect of acidic fluoride solution on NiTi archwires by testing crystal structure, tensile strength, morphology after fracture, and element release from wire under four different test solutions after 1- or 3-day immersion. It was found that (i) 3-day immersion in a 0.2% NaF with pH 4 solution did not form any new crystal structure; however (ii) tensile strength after immersion changed compared to the as-received wires. It was further found that (iii) element release in the test solution increased as NaF concentration and the period of immersion increased, and as pH valued decreased, and (iv) wires immersed in a 0.2% NaF with pH 4 solution released a several-fold greater amount of elements than wire in a 0.05% NaF with pH 4 solution [109].

The shape transformation behavior in three commercial NiTi orthodontic wires having different transformation temperatures was studied by micro-X-ray diffraction (XRD) by Iijima et al. [110]. Micro-XRD spectra were obtained at three different NiTi wires including bending angles (135°, 146°, and 157°) and three different temperatures (25°C, 37°C, and 60°C). The regions analyzed by micro-XRD were within the separate areas of a given wire specimen that experienced only tensile or compressive strain. The diffraction intensity ratio (M002/A110) between the plane (002) peak in martensite phase and the plane (110) peak in austenite phase of NiTi was used as the index to the proportional of the martensite and austenite phases. It was reported that the ratio of martensite to austenite increased in all three Ni–Ti wires with decreasing included bending angle (greater permanent bending deformation) and was lower within the compression area for all wires at all bending angles than within the tension area [110].

Photocatalytic activity from the reaction of titanium oxide with ultraviolet light has recently gained much attention. In particular, there is a scientific interest in inducing photocatalytic reactions on Ti–Ni alloy, a material used in orthodontic appliances. However, it is believed that inducing a photocatalytic reaction with an amorphous oxide film on the alloy is a difficult challenge. Horiuchi et al. [111] induced a photocatalytic reaction on Ti–Ni alloy by subjecting the latter to electrolytic and heat treatment, and then an antibacterial test as used to examine whether a photocatalytic reaction had been induced. By thickening the titanium dioxide film with electrolytic treatment and then applying heat treatment, the surface oxide film of Ti–Ni alloy was thus modified from amorphous structure to rutile crystal. Furthermore, it was revealed that Ti–Ni alloy had an antibacterial effect by virtue of the photocatalytic reaction. Similar work was done by Sato et al. [112] who investigated whether the photocatalytic function of rutile-type titanium dioxide is applicable for orthodontics brackets. To this end, TiO₂ specimens were compressed and sintered. The esthetic and mechanical properties of TiO₂ material were adequate when compared with other bracket materials. In addition, it had a satisfactory photocatalytic function after high-temperature calcinations. Based on the favorable

results, rutile-type titanium dioxide seemed to be applicable for the fabrication of self-cleaning orthodontic brackets [112].

Removable titanium mini-implants were successfully used as anchorage devices in orthodontics. The early load is necessary to simplify the mini-implant methodology but can lead to failure during osteointegration. The Ti–6Al–4V alloy was used instead of CpTi due to its superior strength. However, the corrosion resistance is low, allowing for metal ion release. The aim was to analyze the immediate loaded mini-implant fixation and to gauge the vanadium ion release during the healing process. Titanium alloy mini-implant was inserted in the tibiae of rabbits. After 1, 4, and 12 weeks, they were submitted to removal torque testing. There was no increase in the removal torque value between 0 and 4 weeks of healing, regardless of the load. Nevertheless, after 12 weeks, a significant improvement was observed in both groups, with the highest removal torque value for the unloaded group. The kidney, liver, and lung were also extracted and analyzed by atomic absorption spectroscopy. In comparison with the control values, the content of V increased slightly after 1 week values, significantly increased after 4 weeks and decreased slightly after 12 weeks. A stress analysis was carried out which enables the prediction of both the torque at which CpTi and Ti–6Al–4V deform plastically and the shear strength of the interface. This analysis reveals that the removal torques for CpTi dangerously approach the yield stress. The results of this rabbit model study indicate that titanium alloy mini-implants can be loaded immediately with no compromise of their stability. The detected concentration of vanadium did not reach toxic levels in the animal model [113]. Rozman et al. [114] assessed mechanical properties of superelastic retracting coil springs for orthodontic use. To reach a goal, a test frame comprising measuring force transducers was developed. For *in vivo* testing, 20 male Wistar rats, 11–12 weeks of age, were used. To simulate human distraction as closely as possible, all the applied superelastic retraction coil springs were modified. Coil springs creating a constant force of 25 cN were then attached between the upper left first molar and upper left incisors. Results showed that the reproducible force of 25 cN was shown over a range of 1–11 mm extension. Results also showed that the distance between aforementioned teeth, measured on days 0, 7, 14, 21, 24, 32, 37, and 40, decreased in the group using superelastic retraction coil springs; on the contrary, in the control group, the distance between the teeth increased during the study [114].

Orthodontic brackets made of CpTi have been proposed [115], which can be fabricated through the metal injection mold technique [116].

9.10 Endodontic Files and Reamers

During the instrumentation of curved canals, inadvertent procedural errors, such as ledging, zip formation, and separation of instruments, occasionally occur [117]. When such problems occur, the root canal morphology is adversely altered. This violates a basic endodontic principle, which is that endodontic preparation should

conform as closely as possible to the general configuration of the original canal [118,119]. The American National Standards Institute/American Dental Association (ANSI/ADA) specification No.28 lists certain torsional property requirements for endodontic files and reamers [120]. Instrument separation is a serious concern in endodontics. Because stainless steel instruments usually deform before they separate, dentists can inspect them for visible signs of instrument deformation. A deformed instrument usually shows severe bending or unwinding of the flutes, indicating that the elastic limit of the metal has been exceeded and that the instrument should be discarded. NiTi endodontic instruments were introduced to facilitate instrumentation of curved canals. NiTi instruments are superelastic and will flex far more than stainless steel instruments before exceeding their elastic limit. This flexibility is an important property that allows preparation of curved canals while minimizing transportation. Despite this increased flexibility, separation is still a concern with NiTi instruments, and they have been reported to undergo unexpected fracture [121,122]. Separation can occur without any visible signs of previous permanent deformation, apparently within the elastic limit of the instrument [122]. This indicates that the NiTi instruments could be deteriorated by low-cycle (or high-stress) fatigue damage.

The torsional properties of stainless steel endodontic files and NiTi superelastic endodontic files were compared by Rowan et al. [117]. File sizes 15, 25, 35, 45, and 55 were subjected to torsional loads in both the clockwise (CW) and counterclockwise (CCW) directions independently. Results showed that stainless steel files had a significantly greater rotation to failure in the CW direction, whereas the NiTi files had a significantly greater rotation to failure in the CCW direction. Despite these differences in rotation to fracture, it was reported that there was essentially no difference between the stainless steel and NiTi instruments in the torque that it took to cause failure in both the CW and CCW directions. Therefore, it was concluded that though the number of CW and CCW rotations to failure differed for the two instruments, the actual force that it took to cause that failure was the same [117]. Pruett et al. [122] studied cyclic fatigue of NiTi engine-driven instruments by determining the effect of canal curvature and operating speed on the breakage of light-speed instruments. A new method of canal curvature evaluation that addressed both angle and abruptness of curvature was introduced. Canal curvature was simulated by constructing six curved stainless steel guide tubes with angles of curvature of 30°, 45°, or 60°, and radii of curvature of 2 or 5 mm. A simulated operating load of 10 g cm was applied. Instruments were able to rotate freely in the test apparatus at speeds of 750, 1300, and 2000 rpm until separation occurred. It was found that (i) cycles to failure were not affected by rotation speeds, (ii) instruments did not separate at the head, but rather at the point of maximum flexure of the shaft, corresponding to the midpoint of curvature within the guide tube, and (iii) cycles to failure significantly decreased as the radius of curvature decreased from 5 to 2 mm and as the angle of curvature increased greater than 30 degrees. Based on these findings, it was concluded that, for NiTi engine-driven rotary instruments, the radius of curvature, angle of curvature, and instrument size are more important than operating speed for predicting separation [122].

Instrumentation of the curved canal remains a challenging task to maintain the curvature while avoiding apical transportation and strip perforation. Tucker et al. [123] quantified the canal wall planning achieved by hand instrumentation using stainless steel files, compared with engine-driven NiTi files in curved canals. Twenty-two mesial roots of extracted human mandibular molars were divided into two groups based on root curvature and length. The mesiolingual canals were instrumented using either stainless steel files in a step-back anticurvature filing method or engine-driven 0.02 taper NiTi files. Ground sections were prepared at 1-, 2.5-, and 5-mm levels from the working length. The mesiobuccal canal was used as an uninstrumented control for predentin character. It was found that there was no significant difference in overall canal wall planning between the two groups and no significant difference at each of the three levels [123]. Coleman and Svec [124] compared step-back preparations in curved canals of resin blocks using NiTi K-files and stainless steel K-files. Forty canals in resin blocks were cross-sectioned at three levels; 1–2 mm from the apical foramen, middle of the curve, and coronal. Direct digital computer images were recorded before and after instrumentation, and superimposition of the images combined with digital subtraction computer software allowed direct measurement of the area instrumented, distance of transportation, and shape analysis. It was found that (i) the area removed by instrumentation was significantly greater for stainless steel files at the middle level and (ii) it took significantly longer to prepare a canal with NiTi files in resin blocks compared to stainless steel [124].

There are various methods to assess the progressive damage due to fatigue cycling by either destructive or nondestructive method. They might include subsequent measurements on hardness, ductility, electrical resistance, density, MOE [125], and dislocation density measurements by X-ray diffraction technique [126]. Files are the most efficient instruments in endodontics for the removal of hard tissue and canal enlargement. If the file is evaluated as nondamaged, it will be sterilized and reused (or recycled) on the next patient. Although the breakage and abandonment of a portion of the endodontic file in the root canal may be considered an option, it may cause many problems for certain types of patients. If the patient is hypersensitive to nickel, an allergic reaction may occur. In a more serious case, the dissolved nickel element will act. Accordingly, it can be speculated that the amount of nickel element dissolved from broken NiTi is likely greater than the level found in the intraoral environment. Even with materials containing potentially harmful elements, there are no scientific standards to assess the cumulative damage on NiTi before mechanical failure occurs. Oshida and Farzin-Nia [127] investigated progressive fatigue damage on two NiTi files (0.25 and 0.35 mm in diameter) under fatigue cycling in a push-pull mode inside the root canal having three different canal curvatures ($\alpha = 25^\circ, 40^\circ, \text{ and } 55^\circ$). Changes in DC electrical resistance was monitored with a Wheatstone's bridge-type galvanometer (4.5 DCV) to an accuracy of 0.001Ω at room temperature. It was concluded that (i) normalized cycle-to-failure is linearly related to the normalized damage parameter (change in resistance) and (ii) all the fatigue-fractured files demonstrated an electric resistance ranging between 35 and $40 \text{ m } \Omega$ [127].

By means of XPS and differential scanning calorimeter (DSC), the applications of plasma immersion ion implantation (PI^3 or PIII) for the surface modification of NiTi rotary instruments were studied [128]. Specimens received nitrogen ion or nitrogen plus argon ion implantation. Results indicated that the surfaces of NiTi were successfully modified by nitrogen PIII, whereby a light golden TiN layer was yielded. Moreover, the PIII technique did not alter the superelastic character of NiTi because it was carried out at near-room temperature. We thus concluded that nitrogen PIII is a promising surface modification technique to improve the surface characteristic of NiTi rotary instruments [128].

9.11 Clamps and Staples

The forming and clinical tests of osteosynthesis clamps in NiTi alloy were described. It was reported that (i) by application of localized heating, a defined change in shape is induced after implantation, which compresses the osteotomy gap and (ii) histological evaluation of the tissue surrounding the clamp shows that the alloy satisfies tissue compatibility needs [129]. The SME NiTi staple with an oval part joining the two prongs provides not only a double-compression permanent effect in the prongs and in the oval part but also provides better stability of the osteosynthesis [130]. Its application in the foot has been studied in 1850 cases since 1986 with few (5%) of the contraindications. It was reported that (i) they are associated to the compression strength of the staple in very osteoporotic bones and in the arthrodesis with important resection of the subchondral and cancellous bones, (ii) they have been used successfully for shaft osteotomies of the first phalanx, but also for first joint arthrodesis, and for middle or hind foot arthrodesis, and (iii) in each of these indications, the use of SME staples results in a great improvement not only concerning the reliability of the osteosynthesis but also in healing time due to the double compression effect [130].

Coronary stents made out of NiTi should not be omitted here. NiTi stents have excellent mechanical properties to provide strength to artery walls. The perfect stent does not exist, and it will probably never exist. However, several approaches have been or are currently under investigation to increase their clinical performance. One of these is the implanting of biodegradable stents made of nontoxic materials. The major clinical complication with stents is restenosis, defined as the blockage of blood flow by the coagulation of blood inside the stent [131]. The Homer Mannalok wire needle localizer was also developed using NiTi's superelastic characteristics [96].

9.12 Stents

A coronary stent is a stainless tube with slots. It is mounted on a balloon catheter in a "crimped" or collapsed state. When the balloon is inflated, the stent expands

or opens up and pushes itself against the inner wall of the coronary artery. This holds the artery open when the balloon is deflated and removed. Coronary artery stents were designed to overcome some of the shortcomings of angioplasty. Angioplasty is a technique that is used to dilate an area of arterial blockage with the help of a catheter with an inflatable, small, sausage-shaped balloon at its tip. Although introduced over two decades ago, angioplasty continues to be the most frequently employed procedure in the cardiac lab (either by itself or in conjunction with other procedures such as coronary stenting). However, coronary angioplasty has two shortcomings. First, the opening created by the procedure is not very smooth because the balloon does not evenly expand all areas that have different degrees of hardness (atheroma is soft, plaques are hard, and mixtures of the two have a medium and uneven degree of hardness). This produces a channel with an irregular shape and a rough surface that is covered with superficial or deep cracks. The irregular surface and the cracks on the inner lining of the artery increase the risk of complete arterial blockage in a very small number of patients. Second, some of the compressed material tends to “spring back” to some degree. This is known as “recoil.” Recoil causes the channel to become smaller shortly after being enlarged by balloon expansion. Moreover, the material within the expanded channel starts to multiply after the channel is expanded. This causes a gradual buildup of material. In 30–60% of cases, the buildup of material can be large enough to cause the blockage to return to its original (or worse) severity. This occurs over a 6-week to 6-month duration of time and is known as restenosis. Like angioplasty, coronary stents physically opens the channel of diseased arterial segments, relieves the recurrence of chest pain, increases the quality of life, and reduces other complications of the disease. Since it is performed through a little needle hole in the groin (or sometimes the arm), it is much less invasive than surgery and can be treated with another needle or percutaneous procedure should the patient develop disease in the same, or another artery in the future (<http://www.heartsite.com/html/stent.html>; <http://en.wikipedia.org/wiki/Stent>). There are several studies on NiTi stents. Kulkarni and Bellamy [132] assessed the ease on insertion, patient tolerance, undesirable side effects, degree of encrustation, and duration of upper tract decompression with a new thermoexpandable shape memory alloy ureteric stent. From November 1996 to October 1998, 15 patients with ureteric strictures were treated with a new nickel–titanium shape-memory alloy stent, the Memokath 051 (Engineers & Doctors A/S, Hornbaek, Denmark). A total of 22 insertions were carried out. The stent has a shaft diameter of 9F and its proximal end expands to 17F. The stent is expanded by injection with sterile water preheated to 50°C. The procedures were carried out under a general anesthetic and patients were allowed to go home the next day. The follow-up protocol included initial intravenous urography at 6 weeks, with assessment of a mid-stream urine sample and renal function tests. These were repeated at 3-month intervals. It was reported that there was complete relief of upper tract obstruction in all patients. No stent-related symptoms (e.g., pain, sepsis, hematuria, or frequency), were noted and no encrustation has occurred so far. It was concluded that (i) early experience with this new stent is very encouraging, (ii) all patients have maintained satisfactory decompression of their upper

tracts with no need for repeated hospitalization for stent changes, (iii) there have been no untoward side effects so far, and (iv) this stent appears to have a valuable place in the long-term management of ureteric strictures; it is probably most suited for malignant ureteric obstruction. Ahlhelm et al. [133] studied the deliverability and safety of a braided, self-expanding, closed-cell nickel–titanium (NiTi) stent (E-volution, Jotec GmbH, Hechingen, Germany) especially designed for the endovascular treatment of carotid artery bifurcation stenosis, with special regard to in-stent stenosis and thrombosis, compared with a laser-cut reference nitinol stent in a porcine model of percutaneous vascular interventions. Eight minipigs received a total of 42 stents: 14 reference stents and 28 E-volution stents. Eleven of the E-volution stents were additionally coated with heparin. Control angiography was obtained immediately before and after vascular intervention as well as 4 weeks after the procedure. It was reported that (i) as confirmed by histology, no in-stent thrombosis was observed, (ii) the E-volution stent, especially when heparin coated, is in line with the comparison to the laser-cut reference stent displaying similar results of angiographic, histologic, and histomorphometric analyses, and (iii) compared with the reference laser-cut stent, the self-expanding nitinol stent (E-volution), with its advanced braiding technology, is feasible and safe. It was further concluded that the high radial resistive force and the advanced braided design with tight stent-strut interstices may be beneficial in terms of plaque stabilization. Nitinol (since this material was developed at the US Naval Ordnance Laboratory, it is called Nickel–Titanium Naval Ordnance Laboratory) self-expanding stents are effective in treating peripheral artery disease, including the superficial femoral, carotid, and renal arteries. However, fracture occurrences of up to 50% have been reported in some stents after one year. These stent fractures are likely due to *in vivo* cyclic displacements. The cyclic fatigue and durability properties of Nitinol-based endovascular stents are discussed in terms of an engineering-based experimental testing program. Pelton et al. [134], combining effects of cardiac pulsatile fatigue and stent-vessel oversizing, had evaluated for application to both stents and stent subcomponents. In particular, displacement-controlled fatigue tests were performed on stent-like specimens processed from Nitinol microtubing. Fatigue data were collected with combinations of simulated oversizing conditions and pulsatile cycles that were identified by computer modeling of the stent that mimic *in vivo* deformation conditions. These data are analyzed with nonlinear finite element computations and are illustrated with strain-life and strain-based constant-life diagrams. The utility of this approach is demonstrated in conjunction with 10 million cycles pulsatile fatigue tests of Cordis SMART Control Nitinol self-expanding stents to calculate fatigue safety factors and thereby predict *in vivo* fatigue resistance. These results demonstrate the nonlinear constant fatigue-life response of Nitinol stents, whereby, contrary to conventional engineering materials, the fatigue life of Nitinol is observed to increase with increasing mean strain [134]. Absorbable metallic stents (AMSs) are a newly emerging cardiovascular technology which has the potential to eliminate long-term patient health risks associated with conventional permanent stents. AMSs developed to date have consisted of magnesium alloys, iron, and materials with inferior mechanical properties to those

used in permanent stents, such as stainless steel and cobalt–chromium alloys. However, for AMSs to be feasible for widespread clinical use, it is important that their performance be comparable to modern permanent stents. To date, the performance of magnesium, iron, and permanent stent materials has not been compared on a common stent platform for a range of stent performance metrics, such as flexibility, radial strength, and recoil. In this study, this comparison is made through simulated bench testing, based on finite-element modeling. The significance of this study is that it allows potential limitations in current AMS performance to be identified, which will aid in focusing future AMS design. This study also allows the identification of limitation in current AMS materials, thereby informing the ongoing development of candidate biodegradable alloys. The results indicate that the AMSs studied here can match the recoil characteristics and radial strength of modern permanent stents; however, to achieve this, larger strut dimensions are required. It is also predicted that the AMSs studied are inferior to permanent stents in terms of maximum absolute curvature and longitudinal stiffness [135].

9.13 MRI Safety and Image Compatibility

Titanium biomaterials are placed inside the human body in various forms and shapes, including intraoral dental implants, all types of orthopedic devices and implants, ENT implants, stents, backbone bar, and staples. The magnetic resonance imaging (MRI) compatibility of these titanium device and implants should be considered here. Magnetic field applications should not be limited only to medical equipment, but should also include goods used daily such as magnetic mattresses [136]. MRI is a technology developed in medical imaging that is probably the most innovative and revolutionary aside from computed tomography. MRI is a three-dimensional imaging technique used to image the protons of the body by employing magnetic fields, radio frequencies, electromagnetic detectors, and computers [137]. For millions of patients worldwide, MRI examinations provide essential and potentially lifesaving information. Some devices, such as pacemakers and neurostimulators, however, have limitations related to MRI safety and may be contraindicated for use with MRI. Even more devices, such as stents, vena cava filters, and some types of catheters and guide-wires, are safe for use with MRI but have limited MRI image compatibility. Some of these devices are simply not well imaged under MRI. Others have properties that interfere with the MRI image by causing an image artifact (distortion) in the area in and around the device, limiting the effectiveness of MRI for assisting placement or diagnostic follow-up on these implants. It may be contraindicated in certain situations because the magnetic field present in the MRI environment may, under certain circumstances, result in movement or heating of a metallic orthopedic implant device. Metals that exhibit magnetic attraction in the MRI setting may be subject to movement (deflection) during the procedure. Both magnetic and nonmagnetic metallic devices of certain geometries may also be subjected to heating caused by interactions with the magnetic field. Of

secondary concern is the possibility of image artifacts that can compromise the procedure and image quality. There are currently several researchers as well as an ASTM committee exploring methods for accurately assessing the MRI compatibility of implant devices. The primary focus of the research has been the measurement of implant movement in response to a magnetic field. Shellock and co-workers [138–140] conducted several studies in which the movement and/or deflection of various orthopedic implants was measured in the high magnetic field (0.3–1.5 T) region of MRI units. The results of these studies show no measurable movement of implants fabricated from cobalt, titanium, and stainless steel alloys. The deflection of selected orthopedic implants in a 3.0 T MRI unit was also examined, and it was found that devices fabricated from cobalt, titanium, and stainless steel exhibited little or no movement/deflection [141]. Ferromagnetic metal will cause a magnetic field inhomogeneity, which, in turn, causes a local void signal, often accompanied by an area of high signal intensity, as well as a distortion of the image. They create their own magnetic field and dramatically alter precession frequencies of protons in the adjacent tissues. Tissues adjacent to ferromagnetic components become influenced by the induced magnetic field of the metal hardware rather than the parent field and, therefore, either fail to process or do so at a different frequency and hence do not generate useful signals. Two components contribute to susceptibility artifact: induced magnetism in the ferromagnetic component itself and induced magnetism in protons adjacent to the component. Artifacts from metal may have varied appearances on MRI scans due to different type of metal or configuration of the piece of metal. In relation to imaging, titanium alloys are less ferromagnetic than both cobalt and stainless steel and induce less susceptibility artifact, resulting in less marked image degradation [142,143].

References

- [1] Ban S. Effect of alkaline treatment of pure titanium and its alloys on the bonding strength of dental veneering resins. *J Biomed Mater Res* 2003;66A:138–45.
- [2] McCracken M. Dental implant materials: commercially pure titanium and titanium alloys. *J Prosthodont* 1999;8:40–3.
- [3] Abe Y, Sato Y, Tajiri T, Akagawa Y, Lambrechts P, Vanherle G. An in vitro wear of posterior denture tooth materials on human enamel. *J Oral Rehab* 2001;28:407–12.
- [4] McCaughey AD. Sandblasting and tin-plating-surface treatments to improve bonding with resin cements. *Dent Update* 1993;20:153–7.
- [5] Chang JC, Powers JM, Hart D. Bond strength of composite to alloy treated with bonding systems. *J Prosthodont* 1993;2:110–4.
- [6] Yoshida K, Taira Y, Matsumura H, Atsuta M. Effect of adhesive metal primers on bonding a prosthetic composite resin to metals. *J Prosthet Dent* 1993;69:357–62.
- [7] Anagnostopoulos T, Eliades G, Palaghias G. Composition, reactivity and surface interactions of three dental silane primers. *Dent Mater* 1993;9:182–90.
- [8] Craig RG. Restorative dental materials. St Louis, MO: Mosby; 1993. p. 517–19.
- [9] Musil R, Tiller H. The adhesion of dental resins to metal surfaces. The kulzer silicating technique. Wehrheim, Germany: Kulzer and Co., GmbH; 1984.

- [10] Mudford L, Curtis RV, Walter JD. An investigation of debonding between heat-cured PMMA and titanium alloy (Ti–6Al–4V). *J Dent* 1997;25(5):415–21.
- [11] Oshida Y, Barco MT. Superplastically formed prosthetic components, and equipment for same. US Patent 6,116,070; 2000.
- [12] Okuno O, Nakano T, Hamanaka H, Kato I. Diffusion bonding to titanium alloys during superplastic forming. *J Jpn Soc Dent Mater Devices* 1991;10:483–91.
- [13] Wakabayashi N, Ai M. A short-term clinical follow-up study of superplastic titanium alloy for major connectors of removable partial dentures. *J Prosthet Dent* 1997;77:583–7.
- [14] Srimaneepong V, Yoneyama T, Wakabayashi N, Kobayashi E, Hanawa T, Doi H. Deformation properties of Ti–6Al–7Nb alloy casting for removable partial denture frameworks. *Dent Mater J* 2004;23:497–503.
- [15] Zhang Z, Tamaki Y, Hotta Y, Miyazaki T. Novel method for titanium crown casting using a combination of wax patterns fabricated by a CAD/CAM system and a non-expanded investment. *Dent Mater* 2006;22:681–7.
- [16] Southan DE. Restorative dental materials. *Met Forum Aust Inst Met* 1980;3:222–7.
- [17] Zinelis S, Tsetsekou A, Papadopoulos T. Thermal expansion and microstructural analysis of experimental metal–ceramic titanium alloys. *J Prosthet Dent* 2003;90:332–8.
- [18] Miura I. Titanium alloys for biomaterials, especially dental materials. *Titanium Zirconium* 1991;38:17–8.
- [19] Zinelis S, Bampagadaki X, Vergos V, Chakmakch M, Eliades G. Bond strength and interfacial characterization of eight low fusing porcelains to cp Ti. *Dent Mater* 2010;26:264–73.
- [20] Oshida Y, Miyazaki S. Dentin bonding system. Part II: effects of crosshead speed. *Biomed Mater Eng* 1996;6:87–100.
- [21] Oyafuso DK, Özcan M, Bottino MA, Itinchoe MK. Influence of thermal and mechanical cycling on the flexural strength of ceramics with titanium and gold alloy frameworks. *Dent Mater* 2007;24:351–6.
- [22] Vázquez VZC, Özcan M, Kimpara ET. Evaluation of interface characterization and adhesion of glass ceramics to commercially pure titanium and gold alloy after thermal- and mechanical-loading. *Dent Mater* 2009;25:221–31.
- [23] Elsaka SE, Swain MV. Effect of surface treatments on adhesion of low-fusing porcelain to titanium as determined by strain energy release rate. *Dent Mater* 2011;27:1213–20.
- [24] Hautaniemi JA, Hero H, Juhanoja JT. On the bonding of porcelain on titanium. *J Mater Sci Mater Med* 1992;3:180–91.
- [25] Watanabe K, Okawa S, Miyakawa O, Nakano S, Honma H, Shiokawa N, et al. Interface reactions between titanium and porcelains during firing. *Jpn J Dent Mater* 1993;12:620–9.
- [26] Suansuwan N, Swain MV. Adhesion of porcelain to titanium and a titanium alloy. *J Dent* 2003;31:509–18.
- [27] Hanawa T, Kon M, Ohkawa S, Asaoka K. Diffusion of elements in porcelain into titanium oxide. *Dent Mater J* 1994;13:164–73.
- [28] Brockhurst PJ. Dental materials: new territories for materials science. *Met Forum Aust Inst Met* 1980;3:200–10.
- [29] Togaya T, Suzuki M, Tsutsumi S, Ida K. An application of pure titanium to the metal porcelain. *Dent Mater J* 1983;2:210–9.
- [30] Adachi M, Mackert JR, Parry EE, Fairhurst CW. Oxide adherence and porcelain bonding to titanium and Ti–6Al–4V alloy. *J Dent Res* 1990;69:1230–5.

- [31] Kimura H, Hornig CJ, Okazaki M, Takahashi J. Oxidation effects on porcelain–titanium interface reactions and bond strength. *Dent Mater J* 1990;9:91–9.
- [32] Nagayama K, Izumi T, Kikui T, Okazaki M, Noguchi H. Porcelain-fused-to-titanium-system—EPMA, ESCA studies on the titanium surface and the interface between titanium and fused porcelain. *J Dent Mater* 1993;12:224–5.
- [33] Oshida Y, Hashem A. Titanium–porcelain system Part 1: oxidation kinetics of nitrided pure titanium, simulated to porcelain firing process. *J Biomed Mater Eng* 1993;3:185–98.
- [34] Oshida Y, Fung LW, Isikbay SC. Titanium–porcelain system. Part II: bond strength of fired porcelain on nitrided pure titanium. *J Biomed Mater Eng* 1997;7:12–34.
- [35] Gilbert JL, Covey DA, Lautenschlager EP. Bond characteristics of porcelain fused to milled titanium. *Dent Mater* 1994;10:134–40.
- [36] K  n  nen M, Kivilahti J. Joining of dental ceramics to titanium by metallic interlayers. In: Vinzencini P, editor. *Proceedings of the seventh international meeting on modern ceramic technologies*. Amsterdam: Elsevier; 1990. p. 41–7.
- [37] D  rand T, Her   H. Bond strength of porcelain on cast vs. wrought titanium. *Scand J Dent Res* 1992;100:84–8.
- [38] Rammensberg P, Aschl I, Pospiech P. Verbundfestigkeit niedrigschmelzender Keramiken zu Titan unter Ber  cksichtigung der Oberfl  chen Konditionierung. *Dt Zahn  rtzl Z* 1990;45:200–3.
- [39] Reyes MJD, Oshida Y, Andres CJ, Barco MT, Hovijitra S, Brown D. Titanium–porcelain system. Part III. Effects of surface modification on bond strengths. *J Biomed Mater Eng* 2001;11:117–36.
- [40] Atsu S, Berksun S. Bond strength of three porcelains to two forms of titanium using two firing atmospheres. *J Prosthet Dent* 2000;84:567–74.
- [41] Oka K, Hanawa T, Kon M, Lee HH, Kawano F, Tomotake Y, et al. Effect of barium in porcelain on bonding strength of titanium–porcelain system. *Dent Mater J* 1996;15:111–20.
- [42] Nergiz I, Meine H-C, Niedermeyer W. Untersuchung zur Schverbundfestigkeit von titankeramischen Systemen. *Dt Zahn  rtzl Z* 1999;54:688–90.
- [43] Newham RC. Mechanical properties of ceramic materials: strength tests for brittle materials. *Proc Br Ceram Soc* 1975;25:281–93.
- [44] White SN, Ho L, Caputo AA, Goo E. Strength of porcelain fused to titanium beams. *J Prosthet Dent* 1996;75:640–8.
- [45] White SN, Caputo AA, Vidjak FMA, Seghi RR. Moduli of rupture of layered dental ceramics. *Dent Mater* 1994;10:52–8.
- [46] Oshida Y, Reyes MJD. Titanium–porcelain system. Part IV. Some mechanistic considerations on porcelain bond strengths. *J Biomed Mater Eng* 2001;11:137–42.
- [47] Eriksson M, Andersson M, Carlstr  m E. Titanium dental copings prepared by a powder metallurgy method: a preliminary report. *Int J Prosthodont* 2004;17:11–6.
- [48] Troia Jr MG, Henriques GEP, Mesquita MF, Fragoso WS. The effect of surface modifications on titanium to enable titanium–porcelain bonding. *Dent Mater* 2008;24:28–33.
- [49] Papadopoulos TD, Spyropoulos KD. The effects of a ceramic coating on the cp Ti–porcelain bond strength. *Dent Mater* 2009;25:247–53.
- [50] Bienia   J, Surowska B, Steh A, Matraszek H, Walczak M. The influence of SiO  –TiO   intermediate coatings on bond strength of titanium and Ti6Al4V alloy to dental porcelain. *Dent Mater* 2009;25:1128–35.

- [51] Elaska S, Hamouda IM, Elewdy YA, Abouelatta OB, Swain MV. Effect of chromium interlayer on the shear bond strength between porcelain and pure titanium. *Dent Mater* 2010;26:793–8.
- [52] Vigolo P, Fonzi F, Majzoub Z, Cordioli G. An in vivo evaluation of titanium, zirconia, and alumina procera abutments with hexagonal connection. *Int J Oral Maxillofac Implants* 2006;21:575–80.
- [53] Vigolo P, Fonzi F, Majzoub Z, Cordioli G. Evaluation of gold-machined UCLA-type abutments and CAD/CAM titanium abutments with hexagonal external connection and with internal connection. *Int J Oral Maxillofac Implants* 2008;23:247–52.
- [54] Ebert A, Hedderich J, Kern M. Retention of zirconia ceramic copings bonded to titanium abutments. *Int J Oral Maxillofac Implants* 2007;22:921–7.
- [55] Baixe S, Fauxpoint G, Etienne O. Microgap between zirconia abutments an titanium implants. *Int J Oral Maxillofac Implants* 2010;25:455–60.
- [56] Klotz MW, Taylor TD, Goldberg AJ. Wear at the titanium-zirconia implant-abutment interface: a pilot study. *Int J Oral Maxillofac Implants* 2011;26:970–5.
- [57] Kum D, Park C, Yi Y, Cho L. Comparison of cast Ti–Ni alloy clasp retention with conventional removable partial denture clasps. *J Prosthet Dent* 2004;91:374–82.
- [58] McGiveney GP, Carr AB. McCracken's removable partial prosthodontics. 10th ed. St. Louis: Elsevier; 1999. p. 258–65
- [59] Vallittu PK, Kokkonen M. Deflection fatigue of cobalt-chromium, titanium, and gold alloy cast denture clasp. *J Prosthet Dent* 1995;74:412–9.
- [60] Sahafi A, Peutzfeldt A, Asmussen E, Gotfredsen K. Bond strength of resin cement to dentin and to surface-treated posts of titanium alloy, glass fiber, and zirconia. *J Adhes Dent* 2003;5:153–62.
- [61] Hedlund S-O, Johansson NG, Sjögren G. Retention of prefabricated and individually cast root canal posts in vitro. *Br Dent J* 2003;195:155–8.
- [62] Akişli I, Özcan M, Nergiz I. Resistance of core materials against torsional forces on differently conditioned titanium post. *J Prosthet Dent* 2002;88:367–74.
- [63] Standlee JP, Caputo AA, Hanson EC. Retention of endodontic dowels: effect of cement, dowel length, diameter, and design. *J Prosthet Dent* 1978;39:400–5.
- [64] Standlee JP, Caputo AA, Holcomb J, Trabert KC. The retentive and stress-distributing properties of a threaded endodontic dowel. *J Prosthet Dent* 1980;44:398–404.
- [65] Kovarik RE, Breeding LC, Caughman WF. Fatigue life of three core materials under simulated chewing conditions. *J Prosthet Dent* 1992;68:584–90.
- [66] Chang WC, Millstein PL. Effect of design of prefabricated post heads on core materials. *J Prosthet Dent* 1993;69:475–82.
- [67] Cohen BI, Condos S, Deutsch AS, Musikant BL. Fracture strength of three different core materials in combination with three endodontic posts. *Int J Prosthodont* 1994;7:178–82.
- [68] Huysmans MC, van der Varst PG. Mechanical longevity estimation model for post-and-core restorations. *Dent Mater* 1995;11:252–7.
- [69] Lepe X, Bales DJ, Johnson GH. Tensile dislodgement evaluation of two experimental prefabricated post systems. *Oper Dent* 1996;21:209–12.
- [70] Burgess JO, Summit JB, Robbins JW. The resistance to tensile, compression, and torsional forces provided by four post systems. *J Prosthet Dent* 1992;68:899–903.
- [71] Cohen BI, Condos S, Musikant BL, Deutsch AS. Retentive properties of threaded split-shaft posts with titanium–reinforced composite cement. *J Prosthet Dent* 1992;68:910–2.
- [72] Levartovsky S, Goldstein GR, Georgescu M. Shear bond strength of several new core materials. *J Prosthet Dent* 1996;75:154–8.

- [73] Stockton LW, Williams PT. Retention and shear bond strength of two post systems. *Oper Dent* 1999;24:210–6.
- [74] Stockton LW, Williams PT, Clarke CT. Post retention and post/core shear bond strength of four post systems. *Oper Dent* 2000;25:441–7.
- [75] Huysmans MC, van der Varst PG, Schafer R, Peters MC, Plasschaert AJ, Soltesz U. Fatigue behavior of direct post-and-core-restored premolars. *J Prosthet Dent* 1997;71:1145–50.
- [76] Cohen BI, Pagnillo MK, Newman I, Musikant BL, Deutsch AS. Effects of three bonding systems on the torsional resistance of titanium-reinforced composite cores supported by two post designs. *J Prosthet Dent* 1999;81:678–83.
- [77] Cohen BI, Penugonda B, Pagnillo MK, Schulman A, Hittelman E. Torsional resistance of crowns cemented to composite cores involving three stainless steel endodontic post designs. *J Prosthet Dent* 2000;83:38–42.
- [78] Bergman B, Lundquist P, Sjögren U, Sundquist G. Restorative and endodontic results after treatment with cast posts and cores. *J Prosthet Dent* 1989;61:10–5.
- [79] Hatzikyriakos AH, Reisis GI, Tsingos N. A 3-year post operative clinical evaluation of posts and cores beneath existing crowns. *J Prosthet Dent* 1992;67:454–8.
- [80] Sorensen JA, Martinoff JT. Clinically significant factors in dowel design. *J Prosthet Dent* 1984;52:28–35.
- [81] Taira Y, Yanagida H, Matsumura H, Yoshida K, Atsuta M, Suzuki S. Adhesive bonding of titanium with a thione-phosphate dual functional primer and self-curing luting agents. *Eur J Oral Sci* 2000;108:456–60.
- [82] Turner CH. Post-retained crown failure: a survey. *Dent Update* 1982;9:221–34.
- [83] Kozono Y, Tajima K, Kakigawa H, Hayashi I, Murakami Y. Pure titanium prefabricated post-compatibility with cast metal core. *Dent Mater J* 1986;5:237–45.
- [84] Schmage P, Sohn J, Özcan M, Nergiz I. Effect of surface treatment of titanium posts on the tensile bond strength. *Dent Mater* 2006;22:189–94.
- [85] Topoleski LDT, Ducheyne P, Cuckler JM. Flow intrusion characteristics and fracture properties of titanium-fibre-reinforced bone cement. *Biomaterials* 1998;19:1569–77.
- [86] James SP, Hasty M, Davies J, Piehler H, Harris WH. A fractographic investigation of PMMA bone cement focusing on the relationship between porosity reduction and increased fatigue life. *J Biomed Mater Res* 1992;26:651–62.
- [87] Rose RM, Litsky AS. Biomechanical considerations in the loosening flip replacement prostheses. Current perspectives on implantable devices, vol. 1. New York, NY: JAI Press; 1989. p. 1–45.
- [88] Topoleski LDT, Ducheyne P, Cuckler JM. A fractographic analysis of in vivo poly (methyl methacrylate) bone cement failure mechanisms. *J Biomed Mater Res* 1998;24:135–54.
- [89] Topoleski LDT, Ducheyne P, Cuckler JM. The effect of centrifugation and titanium fibre reinforcement on fatigue failure mechanisms in poly(methyl methacrylate) bone cement. *J Biomed Mater Res* 1995;29:299–307.
- [90] Sih GC, Berman AT. Fracture toughness concepts applied to methyl methacrylate. *J Biomed Mater Res* 1980;14:311–24.
- [91] Zucari AG, Oshida Y, Moore BK. Reinforcement of acrylic resins for provisional fixed restorations. Part I. Mechanical properties. *J Biomed Mater Eng* 1997;7:327–34.
- [92] Panyayong W, Oshida Y, Andres CJ, Barco TM, Brown DT, Hovijitra S. Reinforcement of acrylic resins for provisional fixed restorations. Part III. Effects of addition of titania and zirconia mixtures on some mechanical and physical properties. *J Biomed Mater Eng* 2002;12:353–66.

- [93] Chu KT, Oshida Y, Hancock EB, Kowolik MJ, Barco MT, Zunt SL. Hydroxy-apatite/PMMA composites as bone cements. *J Biomed Mater Eng* 2004;14:87–105.
- [94] Nakamura A, Wanibe H, Ando K, Iwama A, Kitamura K, Shibata N, et al. Mechanical properties of root canal sealers containing titanium oxide. *J Jpn Soc Dent Mater Devices* 2005;24:287–91.
- [95] Stöckel D. Nitinol medical devices and implants. *Min Invas Ther Allied Technol* 2000;9:81–8.
- [96] Pelton AR, Duerig TW, Berg B, Hodgson D, Mertmann M, Mitchell M, et al. Nitinol medical devices. *Adv Mater Process* 2005;163:63–5.
- [97] Fukuyo S, Sachdeva RCL, Oshida Y, Sairenji E. The perio root implant (PRI). In: Fukuyo S, Sachdeva RCL, editors. *Perio root implant and medical application of shape memory alloy*. Tokyo: Japan Medical Culture Center; 1992.
- [98] Andreasen G. A clinical trial of alignment of teeth using a 0.019 inch thermal nitinol wire with a transition temperature range between 31°C and 45°C. *Am J Orthod* 1980;23:528–37.
- [99] Yoneyama T, Doi H, Hamanaka H, Yamamoto M, Kuroda T. Bending properties and transformation temperatures of heat treated Ni–Ti alloy wire for orthodontic appliances. *J Biomed Mater Res* 1993;27:399–402.
- [100] Edman B, Moeller H. Trends and forecasts for standard allergy in a 12-year old patch test material. *Contact Dermatitis* 1982;8:95–8.
- [101] Oshida Y, Sachdeva R, Miyazaki S, Fukuyo S. Biological and chemical evaluation of TiNi alloys. *Mater Sci Forum Trans Tech Pub* 1990;56/58:705–10.
- [102] Sachdeva R, Miyazaki S. Superelastic NiTi alloys in orthodontics. In: Duerig TW, editor. *Engineering aspects of shape memory alloys*. London: Butterworth–Heinemann; 1990. p. 452–69.
- [103] Sunderman FW. A review of the metabolism and toxicity of nickel. *Ann Clin Lab Sci* 1977;7:377–82.
- [104] Samitz MH, Kleen A. Nickel dematerial hazards from prostheses. *J Am Med Assoc* 1972;223:1159–63.
- [105] Sunderman FW. A review of carcinogenicities of nickel, chromium, and arsenic compounds in man and animals. *Prev Med* 1976;5:279–83.
- [106] Oshida Y, Sachdeva RCL, Miyazaki S. Microanalytical characterization and surface modification of TiNi orthodontic archwires. *J Biomed Mater Eng* 1992;2:51–69.
- [107] Kusy RP, Wilson TW. Dynamic mechanical properties of straight titanium alloy arch wires. *Dent Mater* 1990;6:228–36.
- [108] Yanaru K, Yamaguchi K, Kakigawa H, Kozono Y. Temperature- and deflection-dependences of orthodontic force with Ni–Ti wires. *Dent Mater J* 2003;22:146–59.
- [109] Kwon Y-H, Cheon Y-D, Seol H-J, Lee J-H, Kim H-I. Changes on NiTi orthodontic wired due to acidic fluoride solution. *Dent Mater J* 2004;23:557–65.
- [110] Iijima M, Ohno H, Kawashima I, Endo K, Brantley WA, Mizoguchi I. Micro X-ray diffraction study of superelastic nickel-titanium orthodontic wires at different temperatures and stresses. *Biomaterials* 2002;23:1769–74.
- [111] Horiuchi Y, Horiuchi M, Hanawa T, Sima K. Effect of surface modification on the photocatalysis of Ti–Ni alloy in orthodontics. *Dent Mater J* 2007;26:924–9.
- [112] Sato Y, Miyazawa K, Sato N, Nakano K, Takei Y, Kawai T, et al. Study on fabrication of orthodontic brackets with the photocatalic function of titanium dioxide. *Dent Mater J* 2009;28:388–95.

- [113] Morais LS, Serra GG, Muller CA, Andrade LR, Palermo EF, Elias CN, et al. Titanium alloy mini-implants for orthodontic anchorage: immediate loading and metal ion release. *Acta Biomater* 2007;3:331–9.
- [114] Rozman J, Mrvar P, Drevenšek M, Pečlin P. Evaluation of NiTi superelastic retraction coil springs for orthodontic tooth movement. *Biomed Mater Eng* 2010;20:339–48.
- [115] Sachdeva RCL, Oshida Y. Orthodontic bracket. US Patent 5,232,361; 1993.
- [116] Deguchi T, Ito M, Obata A, Koh Y, Yamagishi T, Oshida Y. Trial production of titanium orthodontic brackets fabricated by sintering metal injection molding methods. *J Dent Res* 1996;75:1491–6.
- [117] Rowan MB, Nicholls JJ, Steiner J. Torsional properties of stainless steel and nickel–titanium endodontic files. *J Endodont* 1996;22:341–5.
- [118] Weine FS, Kelly RF, Lio PJ. The effect of preparation procedures on original canal shape and on apical foramen shape. *J Endodont* 1975;1:255–62.
- [119] Walia H, Brantley WA, Gerstein H. An initial investigation of the bending and torsional properties of Nitinol root canal files. *J Endodont* 1988;14:346–51.
- [120] Council on Dental Materials, Instruments and Equipment, Revised American National Standards Institute/American Dental Association Specification No.28 for root canal files and reamers, type K (revised 1988).
- [121] Glosson CR, Haller RH, Dove SB, del Rio CE. A comparison of root canal preparation using Ni–Ti hand, Ni–Ti engine driven, and K-Flex endodontic instruments. *J Endodont* 1995;21:146–51.
- [122] Pruett JP, Clement DJ, Carnes DL. Cyclic fatigue testing of nickel–titanium endodontic instruments. *J Endodont* 1997;23:77–85.
- [123] Tucker DM, Wenkus CS, Bentkover SK. Canal wall planning by engine-driven nickel–titanium instruments, compared with stainless steel hand instrumentation. *J Endodont* 1997;23:170–3.
- [124] Coleman CL, Svec TA. Analysis of Ni–Ti versus stainless steel instrumentation in resin simulated canals. *J Endodont* 1999;25:332–5.
- [125] Pluvinage GC, Raguette MN. Physical and mechanical measurements of damage in low-cycle fatigue: application for two-level test American Society for Testing and Materials STP811 In: Lankford J, Davidson DL, Morris WL, Wei RP, editors. Fatigue mechanisms. Philadelphia, PA: ASTM; 1983. p. 139–50.
- [126] Weiss V, Oshida Y. Fatigue damage characterization by X-ray diffraction line analysis and failure probability, EPRI AP-4477. EPRI 1986:1–18.
- [127] Oshida Y, Farzin-Nia F. Progressive damage assessment of TiNi endodontic files. In: Yahia L, editor. Shape memory implants. New York, NY: Springer; 2000. p. 236–49.
- [128] Li UM, Iijima M, Endo K, Brantley WA, Alapati SB, Lin CP. Application of plasma immersion on implantation for surface modification of nickel–titanium rotary instruments. *Dent Mater J* 2007;26:467–73.
- [129] Bensmann G, Baumgart F. Osetosyntheseklammern aus Nickeltitan Herstellung, Vorversuche und klinischer Einsatz. *Tech Mitt Krupp* 1982;40:123–34.
- [130] Barouk LS. The double compressive nickel–titanium shape-memory staple in foot surgery. In: Yahia L, editor. Shape memory implants. New York, NY: Springer; 2000. p. 162–73.
- [131] Lévesque J, Dubé D, Fiset M, Mantovani D. Materials and properties for coronary stents. *Adv Mater Process* 2004;162:45–8.
- [132] Kulkarni RP, Bellamy EA. A new thermo-expandable shape-memory nickel-titanium alloy stent for the management of ureteric strictures. *BJU Int* 1999;83:755–9.

- [133] Ahlhelm F, Kaufmann R, Ahlhelm D, Ong MF, Roth C, Reith W. Carotid artery stenting using a novel self-expanding braided nickel-titanium stent: feasibility and safety porcine trial. *Cardiovasc Interv Radiol* 2009;32 [101901027].
- [134] Pelton AR, Schroeder V, Mitchell MR, Gong XY, Barney M, Robertson SW. Fatigue and durability of nitinol stents. *J Mech Behav Biomed Mater* 2008;1:153–64.
- [135] Grogan JA, Leen SB, McHugh PE. Comparing coronary stent material performance on a common geometric platform through simulated bench testing. *J Mech Behav Biomed Mater* 2012;12:129–38.
- [136] Oshida Y, Tuna EB, Aktören O, Gençay K. Dental implant systems. *Int J Mol Sci* 2010;11:1580–678.
- [137] Lauterbur PC. Image formation by induced local interactions: example employing nuclear magnetic resonance. *Nature* 1973;242:190.
- [138] Shellock FG, Crues JV. High field strength MR imaging and metallic biomedical implants: an *ex vivo* evaluation of deflection forces. *Am J Roentgenol* 1988; 51:389–92.
- [139] Shellock FG, Morisoli S, Kanal E. MR procedures and biomedical implants, materials, and devices: update. *Radiology* 1993;189:587–99.
- [140] Shellock FG, Mink JH, Curtin S, Friesman MJ. MR imaging and metallic implants for anterior cruciate ligament reconstruction: assessment of ferromagnetism and artifact. *J Magn Reson Imaging* 1992;2:225–8.
- [141] Shellock FG. Biomedical implants and devices: assessment of magnetic field interactions with a 3.0 tesla MR system. *J Magn Reson Imaging* 2002;16:721–32.
- [142] Shellock FG, Fieno DS, Thompson LJ, Talavage TM, Berman DS. Cardiac pacemaker: *in vitro* assessment at 1.5 T. *Am Heart J* 2006;151:436–43.
- [143] Shellock FG, Crues JV. High field strength MR imaging and metallic biomedical implants: an *in vitro* evaluation of deflection forces and temperature changes induced in large prostheses. *Radiology* 1987;165:150–2.

This page intentionally left blank

10 Fabrication Technologies

10.1 Introduction

There are many conventional and advanced technologies available, including casting, milling, spark erosion, forging, powder metallurgy (P/M), and a combination of milling or spark erosion with laser welding to fabricate medical and dental prostheses, devices, and instruments [1–6]. These technologies discussed in this chapter are based on mechanical, chemical, electrochemical, physical, thermal, and combinations of these fundamental principles.

10.2 Casting

There are unusual features associated with titanium casting. Unlike castings of other metals, (i) there are no commercial titanium alloys developed strictly for casting applications; therefore, all titanium castings have compositions based on those of the common wrought alloys and (ii) titanium castings are equal or nearly equal in strength to their wrought counterparts. The casting of titanium dental appliances was noted in the early 1970s in the works of Waterstratt et al. [7], followed by numerous studies in Japan, Europe, and the United States on the precision casting of dental prostheses, and the development of casting machines and suitable investment materials. There are currently about 10 different systems available for casting titanium [8,9]; the Ohara (atmospheric argon shielded arc melting followed by centrifugal casting) and the Castmatic (pressurized argon shielded arc melting followed by gravity casting accelerated by two atmospheres argon pressure above and one atmosphere vacuum below) are just two examples. These casting machines are designed and manufactured, in particular, to overcome the challenging parameters such as high activity and low density of titanium. It was found that the dental titanium castings which were cast in aforementioned casting machines are susceptible to surface oxygen contamination and possible interactive with the investment material, causing three times higher in surface hardness (about 600 Knoop Hardness Number), whereas the rest of the casting exhibits 200 KHN at 200 μm underneath the surface case [10,11].

Evaluation of titanium casting via radiographic means is a technique that has been found useful in detecting internal porosities [12]. Sprue design in Ti, as in gold casting, is important in the prevention of porosities. The most favorable sprue design was

determined to be a rounded or curved sprue [13]. While many authors discuss porosity as a challenge when casting Ti, one study found that 97% of the removable partial denture (RPD) framework cast was technically acceptable [14]. Cecconi et al. [14] evaluated the degree of porosity via radiographic examination of 300 cast CpTi (grade II) RPD frameworks. A single-chamber, gas pressure Titec 205M casting machine was used. It was reported that (i) no framework was returned for any reason, (ii) 250 out of 300 frameworks were technically acceptable as cast, and (iii) 41 were technically acceptable after laser-welding modifications and 9 were technically unacceptable after casting and needed to be redone.

The castability of titanium and its alloys can be metallurgically improved [15,16]. Since commercially pure titanium has a relatively high melting point (1670°C), metastable β -phase Ti-based alloys have recently been developed to reduce the melting points by adding Cr or Pd (e.g., Ti–20Cr–0.2Si or Ti–23Pd–5Cr by wt%) [17,18]. It was reported that Ti casting was done by the argon-arc melting and subsequently argon or vacuum-pressurized casting of Ti–6Al–4V, Ti–15V, Ti–20Cu, and Ti–30Pd [19], and NiTi, Ti–Pt, Ti–Cr, and Ti–Zr alloys [20], as well as CpTi [21,22]. However, special care must always be taken to control casting defects with titanium (which cannot be totally avoided when using a casting process). Defects include such things as shrinkage cavities, pinholes, or voids, and they are particularly a problem with denture bases [23,24], where the surface area is relatively large compared to the thin thickness. It is important to avoid the creation of an α -layer (or α -case), eliminate porosity, and achieve a good fit of the casting onto a die. Since titanium is an active metal, particularly with oxygen, the investment casting of Ti is adversely affected by reaction of the melt with the atmosphere in the melting or casting chamber, reaction of the melt with the melting crucible, and reaction of the melt with the mold materials [2,25–29]. Even when refractories having thermodynamic stability similar to that of the titanium oxide family are used (such as MgO and Al_2O_3), the very strong reducing power of titanium decomposes such common oxides. The oxygen liberated from the oxide diffuses into the surface of the casting to form a hardened layer (about 200 μm thick), depending on the investment material used [10,11,30].

The castability of CpTi and Ti–6Al–4V alloys castings into Rematitan Plus investment was evaluated at three different mold temperatures. It was reported that Ti–6Al–4V alloy (60.86%) presented a better castability than CpTi (48.44%). For CpTi, the temperature of 530°C presented better castability than at other temperatures, namely 480°C and 430°C. For Ti–6Al–4V, there was a statistically significant difference among the three temperatures: 530°C > 480°C > 430°C [31].

Such an oxygen-rich layer (α -case) possesses several drawbacks, including (i) unnecessary hardness and brittleness [32], (ii) reducing ductility and fatigue resistance [9,33], and (iii) resulting in inferior titanium/porcelain bond strengths [34–36]. Several methods have been evaluated to minimize the formation of this reaction layer, including coating the wax pattern with an oxide that is thermodynamically more stable than the titanium oxides before investing [37]. When a wax pattern was coated with a slurry containing Y_2O_3 powder, it was reported that (i) the surface hardness (25 μm from the cast surface) of cast commercially pure titanium was found to be remarkably reduced (280 Vickers Hardness Number (VHN))

compared to the surface hardness of the uncoated cast Ti (530 VHN) [11] and (ii) use of ZrO_2 reduced the hardness near the cast surface (457 VHN) [38]. Miyakawa et al. [29] investigated reaction layer structures of titanium cast in three molds containing spinel-type oxide ($\text{MgO} \cdot \text{Al}_2\text{O}_3$). For this spinel-oxide mold, the reaction zone consisted of baked product layer and the α -case that the latter was divided into two layers. The outside was stabilized and hardened by a solid solution of Al, whereas the inside was not hardened as much without a solid solution of Al. It was found that, for the investment mixed with magnesium acetate solution, the Al-stabilized α -case with higher hardness value formed on limited surfaces [29]. A novel investment material was developed by Nakamura et al. [39]. Fine particle sizes of alumina (Al_2O_3) and zirconia (ZrO_2) were embedded among relatively large particle size silica (SiO_2) crystals, so that the direct contact between molten titanium and silica can be avoided to a great extent. Zr metal powder was mixed with magnetite (magnesium oxide: MgO) to provide an expansion-controlling mold material [39]. It was also reported that, using a large particle size of colloidal silica as a mixing liquid to phosphate-bonded investment, thermal expansion could be controlled and surface roughness, as well as the surface reaction layer, was improved [40]. Cast titanium for dental crowns has been investigated using the investment (consisting essentially of SiO_2 , $\text{Mg}_2\text{P}_2\text{O}_7$, $\text{SiO}_2 \cdot \text{H}_2\text{O}$, and Mg_2SiO_4), claiming that formation of α -case is reduced [41]. A relatively simple method with an investment casting of titanium was developed with various characteristics (such as arc melting in argon, combination of vacuum and pressure-assisted casting, and shell casting with zirconia), and a three-unit crown was successfully cast. It was, therefore, claimed that the formation of a brittle α -case was avoided [42].

There are several unique melting methods. Traditionally, titanium alloys are melted, refined, and cast into round ingots following two or more runs of the vacuum arc remelting process. Multiple vacuum arc remelting runs are used to homogenize the chemical compositions and, further, in an attempt to overcome two types of melt defects—type I hard α inclusions and high-density inclusions—that are a primary quality concern when producing high-performance titanium alloys. These melt defects, when present undetected at subsurface location, could promote premature fatigue failure in rotating components, shorten the life cycle of a component, and compromise product performance and safety. Sampath [43] introduced a competing melting method as plasma arc cold hearth melting and electron beam (EB) cold hearth melting, followed by a vacuum arc remelting. Melting Ti–Nb, Ti–Ta, or Ti–Zr binary alloy is not easy because of melting point and density differences between Ti and the fact that these alloying elements are large. To overcome this technical problem, a cold crucible levitation melting was developed, using cast molding made of a mixture of alumina cement and calcium zirconate with a lithium carbonate as a liquid, and successful melting without any segregation was reported [44].

There are several studies to characterize the titanium castings: porosity [45], grindability [46–48], and mechanical durability [49]. Porosity is a well-known problem in dental titanium casting, resulting in inferior mechanical properties of dental restorations. Four groups of 20 rectangular wax patterns were fabricated in

CyclarII, Dor-A-Matic, Titec 201F, and EasyTi casting machines. It was found that there were no statistical differences among groups tested; nevertheless, pore distribution among the specimens of the same group as inhomogenous. The results showed that the casting machines produced nonuniform porosity. Tokunaga et al. [46] recognized that cast titanium is a known hard-to-polish material, and its final polishing step is a challenge. The best way to solve this challenge lies in automatic and non-mechanical methods. Accordingly the suitability of large-area EB irradiation was examined. After EB irradiation, favorable results were observed: the cast titanium surface became smooth, the glossiness increased, and corrosion resistance was enhanced. These results were attributed to the low heat conductivity of titanium. With mechanical polishing, this property results in temperature rise and burnout reaction of the titanium surface with oxygen and the abrasives. However, during EB irradiation, the low heat conductivity of titanium was an advantage in raising the surface temperature to the melting point, such that a smooth surface was yielded after solidification. Based on the results, it was concluded that automatic polishing by EB seemed to be a suitable polishing method for metal frameworks of removable dentures [46]. As mentioned previously, the hardened α -case layer inevitably forms on the surface of titanium casting when prepared by investment casting. Because the hardness of the α -case is incomparable to that of the interior structure, the perception exists that the α -case is difficult to remove during cutting, grinding, and polishing [47]. Grindability of cast CpTi and cast Ti–6Al–4V was evaluated by grinding cast specimens incrementally using a SiC abrasive wheel. The α -case on the ductile CpTi can be ground much more easily than its bulk interior structure. In less ductile Ti–6Al–4V, the grinding rate is much higher than of CpTi, and the α -case and its interior structure are at similar levels since the fracture toughness of its α -case and the bulk material are not large enough [47]. A similar work was done by Ohkubo et al. [48] with different result. It was reported that grindability increased as the rotational speed increased. There was no statistical difference in grindability for Ti–6Al–4V specimens either with or without the α -case. Iiyama et al. [49] investigated the effects of casting conditions on the mechanical characteristics of cast titanium, with a special focus on cold temperature (23°C, 200°C, 400°C, 600°C, and 800°C). On tensile strength, a significant decrease was observed at mold temperatures above 400°C. On the durability of cast titanium, which was assessed by simulating the actual clasp movement during a cyclic flexural test, it was found that it decreases as the mold temperature increased. Based on these results, it was recommended to cast at lower mold temperatures in order to produce highly fatigue-proof cast titanium clasps [49].

There are few articles on investment casting of titanium [50,51]. Atwood et al. [50] applied computational modeling tools to assist in design of titanium (CpTi grade I) dental crown. It was reported that macroscale modeling was found to be sufficient to accurately predict the location of the large internal porosity. These shrinkage pores were located in the thick sections of the cusp. The model was used to determine the influence of sprue design on the size and location of these pores. Combining the microscale with macroscale modeling allowed the microstructure and depth of contamination to be predicted quantitatively, indicating that the dissolution of silicon

from the mold into the molten titanium is sufficient to depress the freezing point of the liquid metal such that the crown solidifies to the subsurface. Solidification then progresses inward and back out to the surface through the silicon-enriched near-surface. The microstructure and composition of the near-surface region are consistent with this prediction [50].

10.3 Machining

Conventionally, research and development of dental materials has been focused on casting, with very few activities in machinability, specifically aiming on Computer-Aided Design/Computer-Aided Manufacturing (CAD/CAM) materials. For an ordinary machining process, one should remember that titanium's work-hardening coefficient ($n = 0.05$ for the equation $\sigma = K\varepsilon^n$) is much less than that of 316 (18Cr–8Ni–2Mo) stainless steel ($n = 0.45$), copper ($n = 0.54$), and α -brasses ($n = 0.49$) but with proper technique it can readily be machined or polished to a very fine finish. At the same time, it should be noted that Ti is a poor conductor of heat ($0.16 \text{ cal/cm/s/}^\circ\text{C/cm}^2$ versus 0.71 for gold). While this allows excellent localized electric arc spot welding, it means that during cutting heat will not dissipate quickly [10]. It is also true that the relatively low value of modulus of elasticity (MOE) of titanium causes a tendency for work to move away from the cutting tool. But if one uses a few basic rules—low cutting speeds, high feed rates, copious amounts of cutting fluid, and sharp tools replaced at the first signs of wear—good results are obtainable [10]. In general, poor machinability can arise for various reasons, including high tensile strength, high high-temperature strength, high hardness, large ductility, low value of MOE, high work-hardenability, low thermal conductivity, large thermal expansion coefficient, and large reactivity with tool materials. Among these reasons, low value of MOE, low thermal conductivity, and high reactivity are typified for titanium materials.

Titanium materials have unique machining properties. While the cutting forces are only slightly higher than in machining steels, there are other characteristics that make these alloys more difficult to machine than steels having an equivalent hardness. For example, the chip–tool contact area while turning a titanium alloy is only about one-third to one-half as great as that of turning steel. Also, the thermal conductivity of titanium alloy (21.9 W/(m K)) is about one-fourth of that of steels (80.4 W/(m K)). This combination of a small contact area and the low thermal conductivity result in very high cutting temperatures. At a cutting speed of 100 ft/min , the temperature developed at the cutting edge of a carbide tool is 537°C when cutting a steel, while on the titanium alloy, the temperature can reach 704°C . Hence, the cutting speeds on titanium alloys must be lower in order to maintain a tool–chip temperature below that which results in short tool life [52]. Normally, S, Pb, P, Bi, Te, or rare-earth elements are alloyed to improve the machinability. For Ti materials, it was reported that alloying with Au, Ag, or Cu (as β -eutectoid type) or with Nb or Hf (as β -solid solution type) improved the machinability [53].

For the final polishing of titanium materials as well as titanium casts, chemical polishing and buff-polishing are normally practiced. As a novel polishing method, an alcohol-based electrolyte was used while stirring; the original average roughness of CpTi ($0.38\text{ }\mu\text{m}$) was refined to $0.03\text{ }\mu\text{m}$, and the $0.55\text{ }\mu\text{m}$ original roughness of Ti–6Al–4V was improved to be $0.12\text{ }\mu\text{m}$ [54]. To prevent the implant periodontitis, due to plaque accumulation, a certain portion of dental implants need to be finished as smooth as possible to reduce the surface energy. Kyo et al. [55] developed the electrolytic in-process dressing (ELID) grinding technique to the mirror surface polishing in the neck region of the NiTi alloy in contact with alveolar bone. It was reported that (i) the average surface roughness was 185 nm and the center line surface roughness was 22 nm , indicating that good surface properties can be obtained, (ii) the results of analysis of the ELID ground surface showed oxygen peaks other than the titanium and nickel elements, and (iii) when compared to the ground surface, the Ti peak was found to change only slightly along the depth, while the oxygen peak decreased and the Ni peak increased, indicating that the ground surface is oxidized during the ELID machining [55].

Since all the materials have a finite MOE, plastic deformation due to machining is followed by some elastic recovery when the load is removed. In bending, the recovery is called springback. Springback in forming titanium and titanium alloys increases as the R/T ratio (R represents the bend radius and T is work-metal thickness, hence indicating bendability) and yield strength increases and the elastic modulus decreases, and inversely with forming temperature [56]. Springback in titanium alloys is more difficult to predict than springback in steel, although it depends on the same principles. Differences in the yield strength of various heats in titanium can cause differences in springback; higher stress ratios of yield strength to tensile strength generally result in greater springback. The springback phenomenon is mostly important when orthodontic arch-wires are concerned. Orthodontists usually activate orthodontic wires somewhat into the permanent deformation range. Consequently, the practical working range is considered to be the elastic strain at the yield strength of the wire, namely the quotient of yield strength (σ_{YS}) and MOE. This important property (σ_{YS}/MOE) is termed springback [56].

10.4 Electro-discharge Machining

Electro-discharge machining (EDM), also known as spark-erosion dentistry, has been used in industry for over 40 years as a means of machining hard metals with electrical impulses used to cut metal passively and precisely into various shapes and forms [57]. In 1982, Rubeling and Hans-Albert [58] introduced spark erosion and its application to the dental technology. Spark erosion can be defined as a metal removal process using a series of electrical sparks to erode material from a workpiece in a liquid medium under carefully controlled conditions. It is a pressure-less process which does not transmit heat to the alloy, making it possible to consistently machine-fit in the range of 0.05 mm [59]. The procedure consists of

a tension current passing through an electrode, which produces a burning-away of minute particles. A graphite or copper electrode acts as a tool that invades the piece of the base metal and erodes a negative form in the shape of the electrode. The process is accompanied by sparks generated between the electrode and the restoration. The sparks melt the alloy by heating it to between 3000°C and 5000°C [59,60]. The sparks remove small amounts of the metal substrate within microseconds. The entire process takes place in a dielectric liquid bath that prevents the alloy from burning. Advantages of this technique are (i) it is possible to work without pressure, (ii) no heat is conducted to the object being treated, so parts of the prosthesis which have already been finished with porcelain or acrylic resin will not be damaged, (iii) all parts can be absolutely parallel, (iv) very little surface roughness, and (v) no difficulties with any type of material [58,60,61].

The effect of EDM was evaluated on the corrosion resistance of CpTi (grade II) and Co—Cr dental alloys by the anodic polarization method in Ringer's solution. It was found that (i) EDM demonstrated inferior corrosion resistance compared to conventionally finished surfaces and (ii) the latter being passive in a wider range of potential, demonstrated higher polarization resistance and lower corrosion current density [62].

10.5 CAD/CAM

Anderson and Anderson [63] developed a method by which the principles of spark erosion are combined with a method of machine duplication for CpTi fabricating crowns. The Procera process is based on a precision duplication milling through CAD/CAM, combined with spark erosion and laser welding of the metal frame. Procera is designed for use with titanium and densely sintered alumina, making it possible to produce metal—ceramic crowns or all-ceramic crowns [64]. An alternative to casting Ti for ceramic applications was the development of CAD/CAM machining and spark erosion of Ti [65,66]. The main advantage of this technique is that it overcomes the hardened surface layer that is encountered with Ti castings, therefore, providing adequate porcelain—titanium bonding [67,68]. It was mentioned that adaptation of the current Procera CAD/CAM method using pressed-powder technology in the fabrication of Ti copings has several advantages compared to the original Procera method [69,70]. The original method required at least four milling operations, the outer surface milling of the Ti blank, and milling of three electrodes for spark erosion of the inner form. The powder method needs only two milling operations: one for the enlarged refractory die and other for the outer contour of the coping. Using the spark-erosion process, the milling of the outer contour of the coping is performed on a Ti blank. With the pressed-powder method, the powder is compacted onto the surface of the refractory die and then milled before the sintering, which speeds up the process and reduces wear of the milling tools. Although the spark-erosion process requires careful alignment of the carbon electrodes with the Ti blank in fabricating the coping, with powder

technology the alignment is not critical in the same way. The spark-erosion process is a time-consuming and relatively costly operation. The pressed-powder technology could become a very cost-effective operation. The sintering process takes time; however, when the process is used commercially in creating multiple copings at the same time, it could become cost-effective. Several approaches have been reported in the literature using powder technology in dentistry [69,70].

10.6 Isothermal Forging

Isothermal forging differs from conventional forging in that the temperature of the workpiece is held constant during forging by heating the dies. It is found that the microstructure is affected by isothermal forging in various ways, the most important being the production of a fine-grained, equiaxed structure, free of slip banding. Therefore, by careful control of strain rate and temperature, control of the microstructure (and hence the properties) can be achieved. Forging is a common method of producing wrought titanium alloy articles. Forging sequences and subsequent heat treatment as post-forging heat treatment can be used to control the microstructure and resulting properties of the product. Forging is more than just a shape-making process. The key to successful forging and heat treatment is the beta (β) transus temperature (i.e., 885°C). The higher the processing temperature in the ($\alpha + \beta$) region, the more beta is available to transform on cooling. The solution heat treatment offers a chance to modify or tune the as-forged microstructure, while the age cycle modifies the transformed β -structures to an optimum dispersion [71]. Titanium alloys are known to be very susceptible to their metallurgical background, such that their properties can vary considerably depending on the α (HCP) $\leftrightarrow$ β (BCC) transformation temperature. Microstructural control is basic to the successful processing of titanium alloys. Undesirable structures (grain-boundary alphas, beta fleck, elongated alpha) can interfere with optimum property development. Titanium ingot structures can carry over to affect the forged product. Beta processing, despite its adverse effects on some mechanical properties, can reduce forging costs, while isothermal forging offers a means of reducing forging pressure and/or improving die fill and part detail. The first step is to heat the tooling to the forging temperature. A good deal of progress has been made in this area and tooling sets are now available that can withstand elevated temperatures. A second factor for the success of isothermal forging is the forgeability of the alloy: the lower the temperature needed to forge the alloy, the easier it will be to form at uniform temperature. This is why isothermal forming is easier with β or near- β alloys, which have a much lower β -transus and lower resistance to hot forming [71].

10.7 Superplastic Forming

The phenomenon of superplasticity was first observed over 70 years ago, but active research in this field did not begin until 1960. Since then, superplastic effects have

been reported over 100 material systems [72]. The earliest observations of this unique phenomenon were made in the mid-1940s in Russia when a scientist investigated thermal fatigue and discovered an unusual amount of deformation that could not be explained by the ordinal high temperature creep theory. The extensive research activities were stimulated by the pioneer researchers including Backhofen, Underwood, Greenwood, Sherby, Weiss, Oelshlägel, de Jong, Oshida, and others, beginning in the 1960s. There are several conference proceedings and review books available [73–75]. Superplasticity in metals and alloys is a phenomenon that, by its very uniqueness, has attracted scientists and technologists over a considerable number of years. Superplasticity is the deformation process that produces essentially neck-free elongations of many hundreds of percent in metallic materials deformed in tension. High ductility is also encountered in superplastic alloys during torsion, compression, and indentation hardness testing. Superplasticity can be induced both in materials possessing a stable, ultrafine grain size at the temperature of deformation and in those subjected to special environment conditions, e.g., thermal cycling through a phase change. The former type of superplasticity is called ultrafine grain superplasticity, while the latter type is called transformation superplasticity [76–79]. Superplasticity, a necking-resistant flow which results from a high strain-rate sensitivity, m (m in $\sigma = E\dot{\epsilon}^m$) of flow stress (σ), is generally associated with elongation of 100% or greater in tensile tests. The essential requirements for the occurrence of superplasticity are (1) a temperature greater than 0.5, so that diffusional processes are dominant; (2) equiaxed grains $<10\text{ }\mu\text{m}$ in size, so that flow stresses are low and the grain-boundary sliding contribution to strain is high, and (3) a two-phase microstructure to retard grain coarsening [76,80].

First, there is “micrograin” plasticity, in which very fine-grained materials (grain size: $1\text{--}10\text{ }\mu\text{m}$) exhibit superplastic flow within a narrow elevated temperature range at low strain rates ($10^{-5}\text{--}10^{-3}/\text{s}$). The first disadvantage of the “micrograin” superplasticity is its prerequisite for the metallic materials to be preheat-treated to obtain very fine microstructures. Second, during the superplastic forming (SPF), the original micrograin structure will be coarsened, hence the SPFed articles will exhibit somewhat less mechanical properties than the raw materials. This is the second disadvantage. Mechanistically, micrograin superplasticity is accompanied by high-temperature creep deformation. However, coarsened grain structures exhibit higher resistance against the creep deformation than fine-grained structures. This is a main reason why the strain rate with micrograin superplasticity is low. This is the third disadvantage associated with the micrograin superplasticity. Although the transformation superplasticity requires the material have a phase transformation temperature, the preparation is not required to have a very fine structure. Contrarily, during the SPF the materials subjected to the transformation SPF exhibit the grain refining. Accordingly, the strain rate is much higher ($10^{-3}\text{--}10^{-2}/\text{s}$) than that for the micrograin superplasticity, and the transformation-SPFed article shows higher mechanical properties than those fabricated by micrograin superplasticity [72].

Since ultrafine grain microstructure is a prerequisite for exhibiting superplasticity [81], the superplastic materials are not limited to metallic materials, but they

can include ceramic materials as well as fine powder particles [82,83]. Dense and translucent hydroxyapatite polycrystals ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) with a grain size of $0.64\text{ }\mu\text{m}$ were obtained by hot isostatic pressing (HIP) at 203 MPa and 1000°C for 2 h in argon. The material exhibited superplastic elongation ($> 150\%$) in a tension test at temperatures from 1000°C to 1100°C and at strain rates from 7.2×10^{-5} to $3.6 \times 10^{-4}/\text{s}$. [84].

For the superplastic forging, the material selection for the molds is important from the standpoint of high-temperature strength and oxidation resistance. Ni-based alloy can be used as a mold material for SPF and forging of titanium and its alloys. Although ceramics including SiC and Si_3N_4 exhibit very high-temperature strength over 1000°C , they are prone to break due to the thermal stress and the stress concentration, particularly at corner portions [85]. In order to develop a die for SPF of the sheets of titanium and its alloy into dental prostheses, the $\text{CaO-ZrO}_2\text{-TiO}_2$ system was investigated. A practical ceramic die, which hardly reacted with titanium at about 850°C under vacuum, was made by the following process. The mixture of 20 wt% CaO, 60 wt% ZrO_2 , and 10 wt% MgCl_2 was kneaded together with methanol, slipped into a stainless steel ring fixed on a pattern, and formed under the pressure of about 20 kgf/cm^2 into a green. After drying, the green was sintered at 1150°C for 6 h in air [86]. A lubricant agent should also be properly selected in terms of ease of mold separation and surface flatness of the formed products. In general, a mixture in which glass components comprising SiO_2 , B_2O_3 , CaO, FeO, and water are mixed with xylene is used. Sometimes boron nitride (BN) powder is admixed to the aforementioned mixture [85].

Because of their large commercial significance, isothermal forging and superplastic sheet forming of α/β titanium alloys deserve special mention. Both processes rely on the superplastic nature of the fine, equiaxed α -microstructures developed during substructure deformation processing. These microstructures provide low flow stresses, as well as high values of the strain-rate sensitivity. The superplastic properties of α/β alloys are a result of the fine, two-phase microstructure of equiaxed α and β grains. At appropriate strain rates, these microstructures deform by diffusion-controlled, grain-boundary sliding, thus giving rise to low-flow stresses and high values of the strain-rate sensitivity index, as well as deformed microstructures that retain much of their original equiaxed nature. The presence of two phases helps limit the growth of either, to a large extent, thereby enabling the retention of the plastic properties to large strains. Denture bases are now mainly manufactured by a casting process of Co-Cr or Ni-Cr alloys. Ti-6Al-4V alloy is known as a biocompatible metal and also has high strength and low density, so it seems to be the best material for denture bases. Okuno et al. [87] investigated the feasibility study on the superplastic denture base forming of Ti-6Al-4V. It was demonstrated that (i) the Ti-6Al-4V denture base is SPFed by very simple processes by argon gas pressure (10 kgf/cm^2) at $800\text{--}900^\circ\text{C}$ and (ii) SPFed denture bases of Ti-6Al-4V showed some merits compared with conventionally cast or cold-pressed denture base plates, namely good fitness, light weight, and low producing cost using a smaller number of manufacturing processes [87]. SPF of the Ti-6Al-4V alloy is quite an attractive method of fabricating a

full denture base. However, it is not easy to fabricate a partial denture frame by SPF because a retainer-like clasp cannot be fabricated with it. The thickness of the superplastic denture base cannot be controlled to change partially as in casting. Diffusion bonding (DB), which makes it possible to join the retainer or titanium plate to the denture during the SPF of Ti–6Al–4V alloy denture base was attempted. Pure titanium, Ti–6Al–4V, Ti–20Cr–0.2Si successfully joined the Ti–6Al–4V alloy solders by DB during the SPF. Co–Cr alloys, which were coated in advance with 14K to 20K gold alloy solders, were also joined to the superplastic, forming a Ti–6Al–4V alloy denture base [88].

Applications of superplastic phenomenon can be versatile [80,89,90], including forming, bonding, forming/bonding, sintering, heat treatment, and thermomechanical treatment. Each application is faced to the conventional technology. For example, SPF will be faced to sheet metal molding (press forming) and hot forging, SP bonding will be faced to DB and soldering/brazing, SP sintering will be faced to P/M, metal injection molding (MIM), and the combustion synthesis method, and the SP heat treatment will be faced to carburization, nitriding, and carbo-nitriding as well.

10.8 DB and SPF/DB

Shaping and joining are two fabrication processes fundamental to the manufacturing of metallic structure. Limitations in the efficiency and cost-effectiveness of these basic processes may seriously inhibit the use of an otherwise valuable structural material. Such has been the case with titanium in the aerospace industry. SPF/DB is a new fabrication process which provides an attractive answer to this dilemma [89–91]. Because few systematic studies have been made of the effects of material and process variables on the superplasticity of titanium alloys, the effects of metallurgical and process variables on SPF/DB processes were investigated by Sastry et al. [76]. The alloy, processing schedules, microstructure, time, and strain-rate dependency of the superplasticity indices were given special emphasis. Generalized relations between metallurgical and process parameters for SPF of titanium alloys were determined from a systematic characterization of the superplasticity indices (which are normally strain-rate sensitivity) for several α – β titanium alloys. The generalized relations can be used to adjust superplastic processing parameters without time-consuming forming tests on each alloy lot. Alternatively, if the processing parameter limits are fixed, the generalized relations can be used to specify the grain size and alloy compositional limits for any two-phase titanium alloy [76]. It was concluded that techniques for determining the generalized three-dimensional (3D) plots of the interrelation among flow stress, strain rate, and strain should thus be valuable for evaluating the relative superplasticity of different titanium alloys [76].

The SPF/DB process takes advantage of elevated temperature characteristics inherent in the Ti–6Al–4V alloy. This alloy is endowed with a high degree of

superplasticity and excellent characteristics for DB. Thus, monolithic structures that combine severely formed configurations and joints of parent metal properties may be fabricated from titanium alloy sheet stock to achieve a new level of structural efficiency and cost-effectiveness. Okuno et al. [87] developed an SPF/DB method by inserting intermediate metal foils such as palladium and gold alloy solders between CpTi or Ti–6Al–4V to Ti–6Al–4V denture base under argon pressure of 4 kg/cm^2 and forming temperature at 950°C for 2 h.

SPF/DB can be considered as a near-net shape (NNS)-forming technique. NNS processing offers cost reduction by minimizing machining, reducing part count, and avoiding part distortion from welding. NNS technologies such as flow-forming, casting, forging, SPF, P/M, MIM, 3D laser deposition, and plasma arc deposition have been explored for potential use in tubular geometries and other shapes of varying complexity. It appears that the reduction in cost of a given titanium product will be maximized by achieving improvements in all of the manufacturing steps, from extraction to finishing [92].

10.9 Powder Metallurgy

Even though titanium alloys offer increased performance, the question of cost must be faced. Of the “NNS” processes recently developed or advanced for the purpose of reducing material input and machining for titanium alloy part production, P/M exhibits the widest range of process variations and potential applications, particularly in the aerospace industry. P/M has advantages such as the elimination of casting defects, good yield, less segregation, and short processing. A processing route that results in parts as close as possible to NNS forming reduces the overall cost of these parts. P/M is one of these routes, along with isothermal forging and casting. Sintering has a further advantage when dealing with alloys for which problems of segregation are encountered in traditional metallurgical processes involving melting. There are needs to have porosity for titanium implant surface. To provide appropriate porosity to accommodate the bone ingrowth toward a complete osteointegration, titanium powder can be sintered with certain designed porosity. A major problem with the use of titanium is its cost. One of the ways to overcome this problem is by use of an NNS process such as P/M [93]. A typical P/M process includes blending/mixing sponge fines or master alloy $\rightarrow$ cold isostatic press or mechanical pressing $\rightarrow$ vacuum sintering $\rightarrow$ cold work + anneal, HIP, forging, coining $\rightarrow$ final machining. Sintering reactions and fine structures of the biocomposites prepared from powder mixtures of titanium (α -Ti), hydroxyapatite (HA), and bioactive glass (BG) ($\text{SiO}_2\text{--CaO--P}_2\text{O}_5\text{--B}_2\text{O}_3\text{--MgO--TiO}_2\text{--CaF}_2$) were investigated by X-ray diffraction and transmission electron microscopy. The results showed that complex reactions among the starting materials mainly depended on the initial Ti/HA ratios, as well as the sintering temperatures. And the reaction could be expressed by the following illustrative equation: $\text{Ti} + \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \rightarrow \text{CaTiO}_3 + \text{CaO} + \text{Ti}_x\text{P}_y + (\text{Ti}_2\text{O}) + (\text{Ca}_4\text{P}_2\text{O}_9) + \text{H}_2\text{O}$ [94].

Nanoscale and conventional TiO_2 powders were deposited onto titanium alloy using atmospheric plasma spraying technology. As-sprayed titania (titanium oxide) coatings were treated by H_2SO_4 and HCl solutions at room temperature for 24 h, and the bioactivity was evaluated by simulated body fluid (SBF) tests. Measured X-ray diffraction patterns indicated that as-sprayed titania coatings obtained from both nanoscale and conventional powders were composed of primary rutile, as well as a small quantity of anatase and Ti_3O_5 . The surface of as-sprayed coatings prepared from the conventional powder was rougher than that from nanopowder. After immersion in SBF for 2 weeks, both the acid-treated nano and titania coatings were induced with carbonate-containing hydroxyapatite to form on the surfaces. However, this phenomenon did not appear on the surface of as-sprayed nano and conventional titania coatings. The results obtained indicated that (i) the bioactivity of plasma sprayed titania coatings was improved by the acid treatment and (ii) it had nothing to do with the phase composition and particle size of the original TiO_2 powders [95].

P/M technology can be applied to modify the surface zone of implants. Porous coated Ti–6Al–4V alloy implant systems provide a biocompatible interface between implant and bone, resulting in a firm fixation and potential long-term retention via bony ingrowth. In order for an acceptable porous coating structure, the sintering protocol for Ti–6Al–4V alloy systems often requires that the material be heat-treated above the β -transus (i.e., 885°C). This transforms the as-received equiaxed microstructure, recommended for surgical implants, to a lamellar α – β distribution, which has been shown to have the worst fatigue properties of the most common structures attainable in Ti–6Al–4V alloy. However, postsintering heat treatment may be used to improve these properties by producing microstructures more resistant to crack initiation and propagation. Cook et al. [96] investigated the influence of microstructural variations on the fatigue properties of porous coated Ti–6Al–4V alloy material. Nonporous coated and porous coated Ti–6Al–4V fatigue specimens were subjected to a standard sintering heat treatment to produce a lamellar microstructure. In addition, two postsintering heat treatments were used to produce coarse and fine acicular microstructures. Rotating beam (reversed bending) fatigue testing was performed, and the endurance limits determined for the noncoated and porous coated microstructures. The values determined were 680 MPa (noncoated as-received equiaxed), 394 MPa (noncoated lamellar), 488 MPa (noncoated coarse acicular), 494 MPa (noncoated fine acicular), 140 MPa (porous coated lamellar), 161 MPa (porous coated coarse acicular), and 162 MPa (porous coated fine acicular). The noncoated coarse and fine acicular specimens displayed an approximate 25% increase over the noncoated lamellar specimens. The porous coated coarse and fine acicular specimens showed an approximate 15% improvement over the porous coated lamellar specimens [96].

Sintered Ti–6Al–4V powder compacts potentially to be used in implant applications were prepared using commercially available spherical and angular powders (100–200 μm) within the porosity of 34–54%. The green compact was sintered at 1200°C for 2 h. Results have shown that the yield strength of the powder compact of 40–42% porosity was comparable with that of human cortical bone.

Microscopic observations on the failed compact samples revealed that failure occurred primarily by the separation of interparticle bond regions in the planes 45° to the loading axis [97].

For sintering the green compact, two different heat sources were employed: laser-sintering [98] and spark plasma sintering [99,100]. The shear bond strength of cast, machined, and laser-sintered titanium to dental porcelain was evaluated [98]. It was concluded that porcelain–titanium bond strengths could be improved by using the new laser-sintering technique to produce titanium for prosthodontic applications. Sakamoto et al. [99] used the spark plasma sintering technique to sinter Ti powders of $110\text{ }\mu\text{m}$ in diameter. The sintered compacts had a porosity of 28%, a compressive elastic modulus of 7.9 GPa, and an ultimate strength of 112 MPa. The compressive strength of the compacts was increased to 588 MPa by subsequent annealing in a vacuum furnace at 1000°C for 24 h. The sintered compacts were treated with aqueous NaOH solution and subsequently heated at 600°C . The pretreated compacts showed apatite crystal precipitation in SBF. The amounts of precipitate through the compacts were compared with those of the Ti plates substrates subjected to the same chemical pretreatment. It was confirmed that the amounts of precipitates through the compacts were more than one hundred times higher than those on the Ti plates. It was concluded that the metal porous compacts developed may be used as functional materials for immobilizing functional proteins and/or drugs because the precipitated apatite can adsorb these substances [99]. Nanostructured titanium-based biomaterials with tailored porosity are important for cell adhesion, viability, differentiation, and growth [100]. Newer technologies like foaming or low-density core processing were recently used for the surface modification of titanium alloy implant bodies to stimulate bone ingrowth and improve osteointegration and cell adhesion, which, in turn, play a crucial role in the acceptance of the implants. Nanocrystalline CpTi, Ti–6Al–4V, and other Ti-based alloy powders were prepared by high-energy wet-milling and sintered to either full density or uniform porous bulk specimens by the field-assisted spark plasma sintering (FAST/SPS) [100].

Although this chapter is not relevant to dental/medical applications, it should be worthy to report it here for future potential applications. The titanium sheet metal was fabricated from powder sintering technique. Three methods were employed: sintering followed by cold rolling and annealing, direct hot rolling of the roll-compacted sheet, and hot rolling of multiple layers or roll-compacted sheet [101].

DB phenomenon associated with superplasticity can be applied to the bonding powder particles, resulting in superplastic P/M [89]. Superplasticity in metals has received a considerable amount of attention. However, the possibility that ceramic materials also may show anomalous deformational properties coincident with a phase transformation has been neglected. Examples will be given where ready deformation of ceramic bodies may occur with (i) simple allotropic phase transformation, (ii) eutectic exsolution, (iii) exsolution from solid solution, (iv) exsolution by decomposition of mixed crystal systems, and (v) simple decomposition producing one or more solid-phase products and a gas phase; these will be related to the better known processes in metallic systems. It was demonstrated that alumina,

magnesia, Mg–Cr spinel ($\text{MgO} \cdot \text{Cr}_2\text{O}_3$), zirconia (ZrO_2), TCP, and HAP can be sintered by using their superplastic characteristics (in some cases, accompanied by HIP process) [102,103].

10.10 Metal Injection Molding

MIM technology is an advanced P/M offers NNS shaping and mass production of products of the same design [104–107]. MIM has been used successfully in the industrial field, particularly in watch manufacturing, which requires a precise NNS forming [106]. The recent evolution has been to maximize the content of solid particles and to remove the polymer binder during the sintering. As a consequence, a new powder-forming process has evolved, allowing shape complexity, low-cost forming, and high performance properties. Over the last decades, P/M has made significant contributions as an NNS-forming technology. This new process (termed metal powder injection molding [108]) is begun by mixing selected powders and binders. Among its latest spin-offs, injection molding, usually associated with organic polymers, although its use for metal and ceramic components dates back to World War II, has recently received considerable attention [109]. The MIM process comprises the following sequences: (i) mixing/kneading metal powder, binder, solvent, and lubricant to form the so-called compound, (ii) granulating the compound, (iii) injecting the mixed compound into a mold, (iv) debinding the binding material, and (v) sintering. Metal powder is made mainly of atomized powder. Normally, in order to provide the compound better mobility and sintered products of high density, fine particle powder (particle size ranges from several micrometers to several $10\text{ }\mu\text{m}$) is used. In this technology, the use of microsized powders, allowing for greater packing density, results in higher final densities than those generally achievable by conventional P/M [109].

The binder is added (40–50 vol.% of organic binding substances) and consists of thermoplastic resins such as polyethylene or polypropylene, wax, plasticizer, and lubricant. The principle purpose of mixing the binder is to provide sufficient flow mobility when the compound is injected into the mold. The mixture (or compound) is then granulated and injection molded into a desired shape. The polymer imparts viscous flow characteristics to the mixture to aid forming, die filling, and uniform packing. The molded products are then subjected to debinding by either a heating process or a dissolving process in order to remove the binding material. The atmosphere used in the debinding stage includes nitrogen, air, vacuum, wet hydrogen, and hydrogen with hydrochloric acid [110]. The debonded mold is, at the final stage of the MIM process, sintered in either a vacuum or an inert gas such as argon or nitrogen gas. The maximum sintering temperature depends on the type of metal powder. For example, Fe-based alloys are generally sintered in a range from 1200°C to 1400°C . At this moment, the debonded mold is subject to shrinkage. It is reported that the linear shrinkage for Fe-based alloys is 13–20% [110]. However, the shrinkage is approximately linear because the molded product is uniformly filled with metal powder [106]. The product may then be further densified, heat treated, or

machined to complete the fabrication process if required. The application of the MIM method to fabricate the orthodontic bracket was successfully introduced [106].

10.11 Mechanical Alloying

Mechanical alloying (MA) is akin to metal powder processing, where metals may be mixed to produce superalloys. MA is a solid-state powder-processing technique involving repeated cold welding, fracturing, and rewelding of powder particles in a high-energy ball mill. Originally developed to produce oxide-dispersion strengthened Ni- and Fe-based superalloys for applications in the aerospace industry. MA has now been shown to be capable of synthesizing a variety of equilibrium and nonequilibrium alloy phases starting from blended elemental or prealloyed powders. MA occurs in three steps. First, the alloy materials are combined in a ball mill and ground to a fine powder. An HIP process is then applied to simultaneously compress and sinter the powder. A final heat treatment stage helps remove existing internal stresses produced during any cold compaction that may have been used. This produces an alloy suitable for high heat turbine blades and aerospace components. The MA technique allows alloying of elements that are difficult or impossible to combine by conventional melting methods. In general, the process can be viewed as a means of assembling metal constituents with a controlled microstructure. If two metals will form a solid solution, MA can be used to achieve this state without the need for a high-temperature excursion. Conversely, if the two metals are insoluble in the liquid or solid state, an extremely fine dispersion of one of the metals in the other can be accomplished. The process of MA was originally developed as a means of overcoming the disadvantages associated with using P/M to alloy elements that are difficult to combine (<http://www.answers.com/topic/mechanical-alloying#ixzz24UPI5mvZ>).

In the past decades, systematic researchers have been focused on studying Ti–Nb-based Shape Memory Alloys (SMAs) by adding ternary elements, such as Mo, Sn, Zr, etc. However, only arc melting or induction melting methods, with subsequent hot or cold rolling, were used to fabricate these Ni-free SMAs. There is no work related to P/M and porous structures [111]. SMA Ti–22Nb–6Zr (9 at.%) was prepared using elemental powders by means of MA and HIP. It was found that the porous Ti–22Nb–6Zr alloys prepared by the HIP process exhibit homogenous pore distribution with spherical pores, while the pores have irregular shape in the specimen prepared by conventional sintering. The thus obtained Ti–22Nb–6Zr exhibited a superior superelasticity with maximum recoverable strain of $\sim 3\%$ and high compressive strength [111].

10.12 Laser Processing

Applications of laser (light amplification by stimulated emission of radiation) energy are versatile, including engineering applications (forming, honing, welding,

surface modification, cutting), caries detection and oral surgery in dentistry, and various types of microsurgeries in the medical field. With laser welding, it is possible to join parts by the self-welding of the metal parts themselves. Laser technology and laser application have advanced remarkably. Lasers can be made to heat, melt, or vaporize materials, depending on laser power density. Materials absorb power more readily from Nd:Yag laser beams ($\lambda = 1.06 \mu\text{m}$) than they do from CO_2 laser beams ($\lambda = 10.6 \mu\text{m}$). By heating materials, materials can be annealed, or solid-state phase-transformation hardened. Using melting, materials can be alloyed, clad, grain refined, amorphatized, and welded. Using vaporization, materials can be thin film deposited, cleaned, textured, and etched. Using shocking, materials can be shock hardened/peened [112]. Recent advances in the Nd:Yag and CO_2 lasers have made possible a wide range of applications and emerging technologies in the computer, microelectronics, and materials fields. In the realm of materials processing, surface treatments and surface processing, surface treatments and surface modification for metals and semiconductors are of particular interest. With appropriate manipulation of the processing conditions (e.g., laser power density or interaction time), a single laser can be used to perform several processes [113,114].

10.12.1 *Welding*

The potential advantages of laser welding are the following: (1) light is inertialess, hence processing speeds with very rapid stopping and starting become possible, (2) focused laser light can have high-energy density, (3) welding can be achieved at room temperature, (4) difficult materials (e.g., Ti, quartz, etc.) can be handled, (5) the workpiece need not be rigidly held, (6) no electrode or filler materials are required, (7) narrow welds can be made, (8) very accurate welds are possible, (9) welds with little or no contamination can be produced, (10) the heat affected zone (HAZ) adjacent to the cut or weld is very narrow, (11) intricate shapes can be cut or welded at high speed using automatically controlled light deflection techniques, and (12) time sharing of the laser beam can be achieved [115]. The development of high-power lasers has made possible a variety of material removal techniques. Straight line cutting and hole drilling can be done with lasers. Laser turning and milling can also be performed. Two approaches are considered: laser-assisted machining, in which a laser beam heats materials by a single point cutting tool, and laser machining, in which the laser forms a groove in the material by vaporization [116].

Although numerous studies have been made on the use of lasers for welding other dental metals [117–120], few have been made on the welding of titanium materials [121]. Ordinarily, the metal parts of prosthetic devices are soldered by the investment method. However, this procedure is relatively complex and time consuming. Since a laser is capable of concentrating high light energy on a small spot, the possibility of using a laser for joining the precise and miniature parts of prosthetic devices was assessed. Welding experiments were carried out by using a normal pulse, Nd:Yag laser processing apparatus to weld titanium, which is being

used frequently in dentistry. Laser welding of titanium must be carried out in an argon atmosphere. When titanium was irradiated in an atmosphere of ordinary air, cracks appeared in the metal surface, welds cracked, and the mechanical properties of the metal were debilitated. Greater tensile strength, yield strength and elongation of titanium were generally observed with increases in laser irradiation power. Even in an argon atmosphere, the intensity of the laser irradiation must be at least 21 J/P to maintain the tensile strength and yield strength of the original metal. Differences in the laser irradiation atmosphere significantly affected the elongation of titanium [117,121]. With laser welding, it is possible to join parts by the self-welding of the metal parts. However, the laser welding in some occasions induces volume reduction. In order to minimize the volumetric reduction, thin titanium foil was inserted between the titanium plates. It was found that laser-welded titanium plates produced porosity both on the surface and in the cross-sectional areas. Yamakura et al. [122] evaluated the insertion of a titanium foil to be effective in preventing volume reduction during the welding process. It was reported that (i) no porosity was found at the weldment with thin foil insertions, (ii) greater bending strength was generally observed for self-welding titanium plates using 30 μm titanium foil; however, (iii) the bending strength decreased as the thickness of titanium foil was increased, and (iv) laser-welded titanium plates decreased in elasticity, with hardness of the welded area being higher than the original unwelded area [122].

With the introduction of new techniques for the fabrication of titanium frameworks for implant-supported prostheses comes the need to understand how the components used compare to those used for conventional cast frameworks. The relationship of measured machining tolerances between conventional implant components and those components use for stereo laser-welded frameworks was determined using a standardized protocol. It was reported that statistically significant differences in the horizontal interface relationship were found between paired implant components, which had a mean range from 23.1 to 51.7 μm [123].

The obvious differences in structure and properties of the samples by the welding process can be explained by the differing duration of the welding processes. The finding is that laser welding affects the surrounding material only minimally. However, the optimal result will only be achieved if the most suitable energy and duration of the laser impulse are chosen. The large HAZ seen in plasma-welded samples may be attributed to the long and continuous plasma-welding process as well as its difficult manual execution [121]. Roggensack et al. [124] investigated two different methods of welding. Specimens machined from CpTi rods were fused either by laser welding or plasma welding. Hardness profiles and light microscopy images were taken in the region of the weld. The mechanical properties were tested by an alternating bending fatigue test of up to 3×10^6 cycles. Light microscopy images and hardness profiles showed a larger HAZ after plasma welding compared to laser welding. No significant differences comparing fatigue strength could be found between the two methods of welding. Scanning Electron Microscope images of the laser-welded joints showed fractures in the welding zone, while the plasma-welded specimens fractured mostly beyond the HAZ. It was, therefore, concluded that (i) both methods are suitable for welding Ti and (ii) the laser welding is the

more suitable technique in dentistry because of its lower heat effect on the work-pieces [124].

If a clasp on an RPD is damaged or broken, the entire prosthesis may become unstable, lose retention, and become a source of discomfort to the patient. Clasps may be repaired by soldering with a conventional torch technique. However, there are some disadvantages of soldering [121,124,125–127]: (1) the soldered clasp is likely to break again because of stress concentration, (2) discoloration caused by electric and chemical corrosion may occur, (3) soldering of commercially pure Ti is difficult because of oxidation problems, (4) use of fire and gas may be hazardous, (5) technical skill is necessary, and (6) heating may burn the denture base resin. Laser welding is an attractive alternative method to join dental casting alloys [125–127]. During the past decade, laser welding has been increasingly used because there is no need for investment and soldering alloy, working time is decreased, lasers are easy to operate, little damage is caused to the denture resin from the pin-point heat, and there are few effects of heating and oxidation [124]. The penetration depth of the weld into Ti is significantly greater than into gold alloy [127]. Ti has lower thermal conductivity and a greater rate of laser beam absorption compared with gold alloy [127]. These properties make it easier to laser weld Ti to repair broken Ti clasps.

Iwasaki et al. [128] investigated the distortion of laser-welded Ti plates for different operating conditions of the laser-welding devices and with different welding parameters (weld points and prewelding). Nd:Yag laser was used to join CpTi (grade II) plates. Weld surfaces were sand-blasted with 50 μm alumina under 0.2 MPa pressure. It was found that (i) distortion increased stepwise after each welding point along the welding zone (one-side welding), but decreased consecutively as the welding proceeded on the second side of the weld (two-side welding), (ii) in the case of one-side welding, the dependence of distortion on current and spot diameter presented maxima, (iii) for two-side welding, the same parameters exercised little influence on its distortion recovery due to the effect of the solidified weld pool from the first side, and (iv) four-point prewelding significantly decreased the final distortion for both one- and two-side welds [128].

Mechanical properties of laser-welded castings of Ti–6Al–7Nb alloy, CpTi and Co–Cr alloy were investigated and compared to the unwelded castings using a tensile test. A Nd:YAG laser welding was conducted at 220 or 260 laser voltage. The mechanical strength of 260 V was higher than that of 220 V. It was shown that mechanical strength of laser-welded titanium materials was as high as that of unwelded castings, while the mechanical properties of laser-welded alloy joints were influenced by microstructural changes [129]. Similar work was done on comparative study on torsional, ductility, and fracture characteristics of the same materials [130], and it was reported that none of the laser-welded Ti–6Al–7Nb and CpTi castings was broken within the welded joint, showing torsion strength as high as unwelded castings. The effect of irradiation conditions on deformation behavior of pure titanium frames in laser welding was investigated [131]. Two CpTi specimens were abutted against each other to form a welding block with gypsum. Deformation of the specimen caused by laser welding was measured as a rise from

the gypsum surface at the opposite, free end of the specimen. It was observed that specimens with a beveled edge registered a smaller deformation than specimens with a square edge. In addition, a double laser pulse waveform—whereby a supplementary laser pulse was delivered immediately after the main pulse—resulted in a smaller deformation than with a single laser pulse waveform [131]. Furthermore, fatigue performance of laser-welded CpTi joints was investigated [132]. Joint specimens were subject to cyclic tests and the number of cycles to failure was recorded. It was reported that CpTi frameworks with thin diameters, laser welding is better when the structures are juxtaposed [132].

10.12.2 Forming

Laser energy is not only applied to welding, but also to forming or peening technology, being similar to shot forming and shot peening. Laser forming (Lasform) is a laser direct metal deposition process that combines high-power laser cladding technologies with advanced rapid prototyping methods to directly manufacture complex 3D components. Mechanical test data and compositional analysis have shown that the laser-deposited material meets ASTM specifications for CpTi, Ti–6Al–4V, and Ti–5Al–2.5Sn. The system itself is comprised of a large processing chamber, a 14kWCO₂ laser, and a powder-feed system that provides consistent powder flow at high mass-flow rates. Lasform is an additive process and can create NNS geometries requiring minimal post-machining and heat treatment [133]. Laser peening (which is characterized by a contamination-free and noncontact peening for surface hardening) is a process in which a laser beam is pulsed upon a metallic surface, producing a planar shockwave that travels through the workpiece and plastically deforms a layer of material. The depth of plastic deformation and resulting compressive residual stress are significantly deeper than possible with most other surface treatments [134]. These compressive layers are typically 1.0 mm thick, compared with typical depths of 0.25 mm for standard shot peening. As example of laser peening on Ti–6Al–4V, it was reported that the surface compressive residual stress (which is particularly beneficial for enhancing fatigue strength as well as fatigue life) was 830 MPa, and at even 0.25 mm beneath the surface, remained at half of the surface compressive stress (400 MPa) as a compressive internal stress [135].

Direct laser forming (DLF) is a rapid prototyping technique which enables prompt modeling of metal parts with high bulk density on the base of individual 3D data, including computer tomography models of anatomical structures. Hollander et al. [136] investigated DLFed Ti–6Al–4V for its applicability as hard tissue biomaterial. It was reported that rotating bending tests revealed that the fatigue profile of post-DLF annealed Ti–6Al–4V was comparable to cast/hot isostatic-pressed alloy. In an *in vitro* investigation, human osteoblasts were cultured on nonporous and porous blasted DLFed Ti–6Al–4V specimens to study morphology, vitality, proliferation, and differentiation of the cells. It was reported that (i) the cells spread and proliferated on DLFed Ti–6Al–4V over a culture time of 14 days, (ii) on porous specimens, osteoblasts grew along the rims of the pores and formed circle-shaped structures, as visualized by live/dead staining, as well as

scanning electron microscopy, and (iii) overall, the DLFed Ti–6Al–4V approach proved to be efficient, and could be further advanced in the field of hard tissue biomaterials [136].

Laser-engineered net shaping or LENS [137] is a newly developed technology for fabricating metal parts directly from a CAD solid model by using a metal powder injected into a molten (MIM) pool created by a focused, high-powered laser beam (HPLB). A high-power laser is used to melt metal powder supplied coaxially to the focus of the laser beam through a deposition head. The laser beam typically travels through the center of the head and is focused to a small spot by one or more lenses. The X–Y table is moved in raster fashion to fabricate each layer of the object. The head is moved up vertically as each layer is completed. Metal powders are delivered and distributed around the circumference of the head either by gravity, or by using a pressurized carrier gas. An inert shroud gas is often used to shield the melt pool from atmospheric oxygen for better control of properties, and to promote layer-to-layer adhesion by providing better surface wetting. The LENS process is unique since it can go from raw material directly to metal parts, in many cases, without any secondary operations. It can produce parts in a wide range of alloys, including titanium, stainless steel, aluminum, and other specialty materials, as well as composite and functionally graded materials. Primary applications for LENS technology include repair and overhaul, rapid prototyping, rapid manufacturing, and limited-run manufacturing for aerospace, defense, and medical markets [137].

10.12.3 *Machining*

Laser energy can also be applied to various engineering fields, including processing, shaping, machining, or coating [137–140]. Pulsed laser deposition (PLD) is a physical vapor deposition (PVD) process for creating diamond-like carbon thin films. PLD is a thin film deposition (specifically a PVD) technique where a high-power pulsed laser beam is focused inside a vacuum chamber to strike a target of the material that is to be deposited. This material is vaporized from the target (in a plasma plume) which deposits it as a thin film on a substrate (such as a silicon wafer facing the target). The ejected species expand into the surrounding vacuum in the form of a plume containing many energetic species including atoms, molecules, electrons, ions, clusters, particulates, and molten globules, before depositing on the typically hot substrate [138].

Laser micromachining is a general term that includes a variety of processes including hole drilling, ablation, milling, and cutting, and process is to offer picosecond laser micromachining which can process metals, polymers, and ceramics with no peripheral damage. This equipment uses CAD geometry to direct-write the customer-required geometry. For the defense industry, example applications include microair vehicle components fabrication, surface texturing of aircraft components, and vehicle health monitoring sensors (<http://www.mlpc.com/laser-micromachining-services?gclid=C1b55vKkgbICFWXhQgodsC0AuA>). Recently,

the femtosecond-laser-based tooth preparation technique has been developed [141–143] (www.mdatechnology.net/techsearch.asp?articleid=191).

Laser alloying is a material-processing method that utilizes the high-power density available from focused laser sources to melt metal coatings and a portion of the underlying substrate. Since the melting occurs in a very short time and only at the surface, the bulk of the material remains cool, thus serving as an infinite heat sink. Large temperature gradients exist across the boundary between the melted surface region and the underlying solid substrate. This results in rapid self-quenching (10^{11} /ks) and resolidification (velocities of 20 m/s). What makes laser surface alloying both attractive and interesting is the wide variety of chemical and microstructural states that can be retained because of the repaid quench from the liquid phase. The types of observed microstructures include extended solid solutions, metastable crystalline phases and metallic glasses as an amorphous metal [144,145]. Alloy production with a wide variety of elements, as well as a wide range of compositional content, can also be accomplished by an MA or P/M, both of which do not involve liquids.

10.12.4 Surface Treatments

The sol–gel process is a wet-chemical technique widely used in the fields of materials science and ceramic engineering. Such methods are used primarily for the fabrication of materials (typically metal oxides) starting from a colloidal solution (sol) that acts as the precursor for an integrated network (or gel) of either discrete particles or network polymers. Typical precursors are metal alkoxides and metal salts (such as chlorides, nitrates, and acetates), which undergo various forms of hydrolysis and polycondensation reactions. A novel sol–gel/laser-induced technique (SGLIT) has been developed to form nanocrystalline titanium dioxide (TiO_2)-based thin films with an improved antibacterial performance [146]. TiO_2 precursor films loaded with W^{+6} and Ag^{+2} ions (W-TiO_2 , Ag-TiO_2) were prepared separately by sol–gel method and spin-coated on microscopic glass slides. As-dried films were subjected to KrF excimer laser pulses at optimized parameters to generate porous anatase and rutile phases at room temperature. It was reported that (i) a crystallite size of approximately 20 nm was achieved from the anatase prepared by SGLIT and (ii) the films exhibited an enhanced antibacterial function against *E. coli* cells under the UV excitation [146].

The effect of laser surface treatment on the mechanical properties of cast titanium was investigated to compare with those of the Co–Cr alloy. Dumbbell-shaped cast specimens were prepared for commercially pure titanium (grade II) and Co–Cr alloy. The cast titanium specimens were laser treated on the surface using a dental Nd:YAG laser machine at 240 and 300 V. After laser treatment, tensile testing was conducted to obtain the tensile strength, percent elongation, and MOE. The hardness depth profile was made from the cast subsurface (25 μm) to 1500 μm in depth using the cross sections of the cast rods with the same diameter as the dumbbell. It was obtained that (i) the highest tensile strength was obtained for the titanium specimens laser treated with 300 V followed by the 240 V and the control

specimens and (ii) the laser-treated titanium specimens with 300 V showed a tensile strength equivalent to the Co–Cr alloy. Although the highest MOE was found for the specimens laser treated with 240 V, there were no significant differences in elastic modulus among 240, 300 V, and Co–Cr. The laser-treated groups showed significantly lower hardness at the subsurface of 25 μm and maintained their hardness until the depth of 400 μm . The hardness of the control group was very high at 25 μm depth and dramatically decreased until the 200 μm depth. Hence, it was concluded that the results of tensile testing and hardness depth-profiling indicated that the laser treatment significantly improved the mechanical properties of cast titanium by improving the surface integrity of the cast surface contamination [147].

Forty-eight threaded CpTi implants with machined surfaces were prepared to compare the bone responses to a pure titanium machined implant surface and one that had been modified by laser etching and microarc oxidation. The control group consisted of 24 implants with a machined surface. The test group consisted of 24 machined-surface implants that were modified by laser etching and treated by microarc oxidation in an electrolyte solution containing Ca^{2+} and $(\text{PO}_4)^{3-}$ ions. The implants were analyzed by energy-dispersive X-ray and scanning electron microscopy. Next, the two types of implants were inserted in the tibiae of 12 New Zealand White rabbits; one of the two tibiae received two control implants and the opposite side received two test implants. After 2, 4, and 6 weeks, the rabbits were sacrificed. All rabbits were injected with fluorescent-labeled achromycin and calcein. Samples were cut and ground for histomorphologic observation, and the mineralization appositional rate and the osteointegration index were measured and analyzed. It was found that (i) proportional spacing craters were found with a diameter of 100 μm and a depth of 80–100 μm at intervals of 100 μm around the test surface and (ii) a porous titanium dioxide coating on the surface with pores of 1–5 μm in diameter was also produced. Carbon, oxygen, calcium, and phosphonium were detected by electronic probe. The ratio of calcium to phosphonium (Ca/P) was 1.418, and the crystal structure of X-ray diffractive patterns indicated pure anatase phases. Compared with the control samples, the mineralization ratio and the osseointegration index of the bone around the test implants were higher. It was concluded that (i) the porous titanium dioxide coating produced by laser etching and microarc oxidation treatment improved the bone response versus that seen around machined titanium implants and enhanced the bone formation rate and (ii) the surface chemistry and topography, either separately or together, play an important role in the bone response to implants [148].

Recently, tantalum is gaining more attention as a new metallic biomaterial as it has been shown to be bioactive and biologically bonds to bone. However, the relatively high cost of manufacture and an inability to produce a modular all Ta implant has limited its widespread acceptance. Ta coating was deposited on Ti using LENS to enhance the osteointegration properties. An *in vitro* biocompatibility study, using human osteoblast cell line hFOB, showed excellent cellular adherence and growth with abundant extracellular matrix (ECM) formation on the Ta coating surface compared with the Ti surface. A living cell density of six times higher than normal was observed on the Ta coating than on the Ti control surface. A high

surface energy and wettability of the Ta surface were observed to contribute to its significantly better cell–material interactions. Also, these dense Ta coatings do not suffer from low fatigue resistance due to the absence of porosity and a sharp interface between the coating and the substrate, which is a major concern for porous coatings used for enhanced/early biological fixation [149].

Load-bearing metal implants often fail prematurely due to inadequate biocompatibility, mechanical/tribological properties, and poor osseointegration. It is well known that biomaterials' surface plays a vital role in response to these metal implants in the biological environment. The biological effectiveness of artificial implants is determined mainly by their surface characteristics such as surface morphology, microstructure, composition, mechanical properties, wettability, and surface free energy. Hence, there is significant interest in surface modification and effective design of load-bearing metal implants so as to improve their surface properties and thereby elicit a specific, desired, and timely response from the surrounding cells and tissues. Bandyopadhyay et al. [150] discussed the laser surface modification of CpTi and Ti–6Al–4V alloy with or without functional gradation in composition and their microstructural, *in vitro* wear and biological properties for various load-bearing orthopedic applications.

The effect of an argon-based atmospheric pressure plasma (APP) surface treatment was investigated, operated chairside at atmospheric pressure conditions applied immediately prior to dental implant placement in a canine model [151]. Surfaces studied included rough titanium surface (Ti) and rough titanium surface + argon-based APP (Ti-Plasma). Six adult beagle dogs received two plateau-root form implants in each radii, providing implants that remained 1 and 3 weeks *in vivo*. Histometric parameters assessed were bone-to-implant contact (BIC) and bone area fraction occupancy (BAFO). At 1 week no difference was found in histometric parameters between groups. At 3 weeks significantly higher BIC (> 300%) and mean BAFO (> 30%) were observed for Ti-Plasma treated surfaces. It was concluded that, from a morphologic standpoint, improved interaction between connective tissue was observed at 1 week, likely leading to more uniform and higher bone formation at 3 weeks for the Ti-Plasma treated implants was observed [151].

10.13 Friction Stir Welding

Friction stir welding (FSW) is a solid-state joining process and is used for applications where the original metal characteristics must remain unchanged. It works by mechanically intermixing the two pieces of metal at the place of the join, transforming them into a softened state that allows the metal to be fused using mechanical pressure, much like joining clay or dough. This process is primarily used on aluminum, and most often on large pieces which cannot be easily heat-treated post-weld to recover temper characteristics. FSW is the most recent upgrade to the Space Shuttle's gigantic External Tank, the largest element of the Space Shuttle and the only element not reusable. The new welding technique—being marketed to

industry—utilizes frictional heating combined with forging pressure to produce high-strength bonds virtually free of defects [152] (<http://www.springerlink.com/content/u6741863473kn56/fulltext.html>).

10.14 Soldering

Although there are several disadvantages of soldering, titanium materials are frequently employed in dentistry, and their solder joining is often conducted. Like as other technologies involving elevated temperatures with titanium materials, the joining portion is appropriately sealed from the ambient atmosphere to avoid unwanted oxidation. Solder strength normally depends on various factors, such as the solder material's mechanical strength, extent and completion of diffusion into the base material, penetration and cavity at the soldering interface, and the base material's strength. Heat effect on the base material (HAZ), as well as the solder, will influence the strength of the prosthesis after the solder process is completed, and corrosion resistance when the prosthesis is used in intraoral environment. Soldering is normally done by electro-resistance soldering, infrared soldering, or plasma soldering, all in an argon atmosphere. It is generally believed that casting and soldering are two major technical difficulties associated with titanium materials because titanium has a relatively high melting point and high reactivity with oxygen. In industry, there are three types of solders used for titanium materials: silver based, aluminum based, and eutectic solders. If appropriate measures are taken in order to control the excessive oxidation, titanium materials can be successfully solder joined in the dental/medical fields. These measures might include material factors (using high activity flux and low melting point solders) and environment factors (nonoxidizing atmosphere and shorter operation time) [153].

10.15 Heat Treatment

For reducing residual stresses (mostly tensile residual stresses) that develop during fabrication, titanium materials are heat treated—stress relieving. For improving mechanical properties (ductility), machinability, and structural stability, titanium products are also heat treated—annealing. For increasing mechanical strength, titanium is heat treated—solution treating and aging. Alpha and near-alpha titanium alloys can be stress relieved and annealed but high strength cannot be developed in these alloys by any type of heat treatment. The β -phase in the commercial beta and metastable beta alloys decomposes at selected elevated temperatures to cause the material to strengthen. Phase compositions, sizes, and distributions can be manipulated by heat treatment within certain limits to enhance a specific property or to attain a range of strength levels [154]. For a certain type of titanium alloy, post-welding heat-treatment (PWHT) is recommended. Development of maximum properties in α – β alloy weldments requires solution treating followed by rapid

quenching and then aging. However, if reduced strength is acceptable or higher ductility is required, workpieces may be annealed only, after welding.

The microstructural evolution and attendant strengthening mechanisms in two novel orthopedic alloy systems, Ti–34Nb–9Zr–8Ta and Ti–13Mo–7Zr–3Fe, have been compared by Banerjee et al. [155]. In the homogenized condition, both alloys exhibited a microstructure consisting primarily of a β -phase matrix with grain-boundary α -precipitates and a low-volume fraction of intragranular α -precipitates. On aging of the homogenized alloys at 600°C for 4 h, both alloys exhibited the precipitation of refined scale secondary α -precipitates homogeneously in the β -matrix. However, while the hardness of the Ti–13Mo–7Zr–3Fe alloy marginally increased, that of the Ti–34Nb–9Zr–8Ta alloy decreased substantially as a result of the age treatment. In order to understand this difference in the mechanical properties after aging, Transmission Electron Microscope studies were carried out on both alloys prior to and post-aging. It was reported that a metastable B2 ordering in the Ti–34Nb–9Zr–8Ta alloy was found in the homogenized condition which is destroyed by the aging treatment, consequently leading to a decrease in the hardness [155].

10.16 Coating

The twin wire arc spray (TWAS) is a novel coating method to spray coating material using compressed air as the atomizing gas in open air spray distances near six inches; the coupons were rotating on a fixture, and the spray gun was mounted. Controlling the arc gap is another essential part of the process, and without this arc gap control, the wires will actually interfere with the atomizing process and cause a mix of large and small splats and thereby increase porosity. TWAS produces coatings of less than 0.3% porosity for 420SS, and 0.04% porosity for the coating of Inconel 625. The coatings were sprayed using ordinary compressed air as the atomizing gas in open air with spray distances near six inches. The coupons were rotated on a fixture and the spray gun was mounted. In this process, the high electric arc energy from the two consumable wires heats gas inside a small vessel that is pressurized by both ionization and hot expanding gas. A jet stream exits a small port in front of which the wires are positioned and then melted, atomized, and propelled to the substrate (www.thermioninc.com).

Franco et al. [156] evaluated bone response to Ca- and P-enriched titanium surface treated by a multiphase anodic spark deposition coating (BSP-AK). Two mongrel dogs received bilateral implantation of three titanium cylinders in the humerus, being either BSP-AK treated or untreated (machined—control). At 8 weeks postimplantation, bone fragments containing the implants were harvested and processed for histologic and histomorphometric analyses. In most cases, in the medullary area, collagen fiber bundles were detected adjacent and oriented parallel to titanium surfaces. Such connective tissue formation exhibited focal areas of mineralized matrix lined by active osteoblasts. The mean percentage of BIC was 2.3% for BSP-AKed, compared to 0.4% for control [156].

Coating of bioceramic material, hydroxyapatite (HA), on metal implants has attracted much attention in the biomedical industry recently because of its combination of good mechanical property and biocompatibility. However, most of the current HA coatings lack coating/substrate interfacial strength, and/or biocompatibility. The cell–tissue attachment is affected by the degraded biocompatibility due to the decomposition of HA during high-temperature processing. Cheng et al. [157] investigated the transmission laser coating (TLC) to coat HA on Ti substrate with low-temperature processing. This process enhances the HA/metal interfacial property of current coatings, while maintaining good biocompatibility. Experiments are conducted using a continuous neodymium-doped yttrium aluminum garnet (Nd-YAG) laser. It was reported that TLC processing will open new ways of producing biocompatible bioceramic coating with controlled thickness and at low temperature [157].

10.17 Electrospinning

The entire process can consist of four steps: step 1, the deposition of the coating fluid onto the wafer or substrate; step 2, the substrate is accelerated up to its final, desired, rotation speed; step 3, the substrate is spinning at a constant rate and fluid viscous forces dominate fluid thinning behavior; and step 4, the substrate is spinning at a constant rate and solvent evaporation dominates the coating thinning. Processing scaffolds that mimic the ECM of natural bone in structure and chemical composition are a potential promising option for engineering physiologically functional bone tissue. Liao et al. [158] reported a novel method, by combining electrospinning and minelarization, to process a series of nanofibrous scaffolding systems with desirable characteristics, namely collagen and poly(lactic-co-glycolic acid) (PLGA), natural and synthetic of its kind, respectively, to electrospin into nanofibrous scaffolds. The electrospun scaffolds have high surface area, high porosity, and a well-connected pore network. In order to mimic the chemical composition of native bone ECM, the electrospun scaffolds were subjected to mineralization under optimal conditions. From the experimental results, it was observed that the formation of bone-like apatite into collagen was relatively abundant and significantly more uniform than PLGA. The major finding has suggested that the surface functional groups of the scaffolding material, such as carboxyl and carbonyl groups of collagen, are important for minelarization *in vitro*. In addition, it was revealed that the mineralization process predominantly induces the formation of nanosized carbonated hydroxyapatite during collagen mineralization, whilst nanosized hydroxyapatite is formed during PLGA mineralization. These findings are critically important while selecting the material for processing a bone scaffolding system [158].

The time required for osteointegration with a metal implant having a smooth surface ranges from 3 to 6 months. PLGA or PLGA/collagen (50:50 w/w ratio) fiber was coated on Ti disks by modified electrospinning for 5 s to 2 min, followed

by depositing nano-HA on the fibers. PLGA fibers of fiber diameter $0.957 \pm 0.357 \mu\text{m}$ had a contact angle of $9.9 \pm 0.3^\circ$ and PLGA/collagen fibers of fiber diameter $0.378 \pm 0.068 \mu\text{m}$ had a contact angle of 0° . Upon nano-HA incorporation, all the fibers had a contact angle of 0° owing to the hydrophilic nature of nano-HA biomolecule. The cell attachment efficiency was tested on all the scaffolds for different intervals of time (10, 20, 30, and 60 min). The alkaline phosphatase activity, cell proliferation, and mineralization were analyzed on all the implant surfaces on days 7, 14, and 21. Results of the cell adhesion study indicated that the cell adhesion was maximum on the implant surface coated with PLGA/collagen fibers deposited with nano-HA compared to the other scaffolds. Within a short span of 60 min, 75% of the cells adhered onto the mineralized PLGA/collagen fibers. Similarly, by day 21, the rate of cell proliferation was significantly higher on the mineralized PLGA/collagen fibers owing to enhanced cell adhesion on these fibers. This enhanced initial cell adhesion favored higher cell proliferation, differentiation, and mineralization on the implant surface coated with mineralized PLGA/collagen fibers [159].

10.18 Electron Beam Melting

Electron beam melting (EBM) is a type of additive manufacturing for metal parts. It is often classified as a rapid manufacturing method. The technology manufactures parts by melting metal powder layer by layer with an EB in a high vacuum. Unlike some metal sintering techniques, the parts are fully dense, void free, and extremely strong. The vacuum environment in the EBM machine maintains the chemical composition of the material and provides an excellent environment for building parts with reactive materials such as titanium alloys. The EB's high power ensures a high rate of deposition and an even temperature distribution within the part, which gives a fully melted metal with excellent mechanical and physical properties. This unique technology is the result of intensive research and development and has a wide array of applications within additive manufacturing. The microstructure and mechanical behavior of simple product geometries produced by layered manufacturing using the EBM process and the selective laser melting (SLM) process are compared with those characteristic of conventional wrought and cast products of Ti–6Al–4V. Microstructures revealed α (hcp), β (bcc), and α' (hcp) martensite phase regimes which give rise to hardness variations ranging from HRC 37 to 57 and tensile strengths ranging from 0.9 to 1.45 GPa [160].

Porous implants for the reconstruction or craniofacial defects have gained importance due to their better performance over the generic counterparts. The recent introduction of EBM for the processing of titanium has led to a one-step fabrication of porous custom titanium implants with controlled porosity to meet the requirements of the anatomy and functions at the region of implantation. The image-based microstructural analysis and the mechanical characterization of porous Ti–6Al–4V structures fabricated using EBM rapid manufacturing process was

discussed [161]. It was observed that the complete melting of the powder material with no evidence of poor interlayer bonding, and samples are well formed within titanium struts and fully interconnected pores with porosities varying from 49.75% to 70.32%. Compression tests of the samples showed effective stiffness values ranging from 0.57 to 2.92 GPa and compressive strength values 7.28–163.02 MPa. The grain density of the fabricated Ti–6Al–4V structures was found to be 4.423 g/cm³ equivalent to that of dense Ti–6Al–4V parts fabricated using conventional methods. In conclusion, from a mechanical strength viewpoint, it was found that the porous structures produced by the EBM process present a promising rapid manufacturing process for the direct fabrication of customized titanium implants [161].

10.19 Additive Manufacturing

Additive manufacturing or 3D printing is a process of making 3D solid objects from a digital model. 3D printing is achieved using additive processes, in which an object is created by laying down successive layers of material. 3D printing is considered distinct from traditional machining techniques (subtractive processes), which mostly rely on the removal of material by drilling and cutting. 3D printing is usually performed using a materials printer. The technology also finds use in the fields of jewelry, footwear, industrial design, architecture, engineering and construction, automotive, aerospace, dental and medical industries, education, geographic information systems, civil engineering, and many others [162] (<http://www.paramountind.com/additive-manufacturing.html>; <http://www.lia.org/conferences/lam>).

The unique application of this technique can be found in fabricating customized implants. The ability to quickly and cost-effectively produce a customized implant has always been appealing from a marketing and manufacturing standpoint. Historical barriers to this becoming a reality have included the inability to properly design a net shape implant in a digital environment and the inability to manufacture the implant in a digital manner. With the advent of better design tools and more options for output in manufacturing materials, providing truly customized implants is possible today (http://www.nist.gov/tip/wp/pswp/upload/129_precision_additive_manufacturing_of_medical_device.pdf). A major biomedical application of additive manufacturing is prosthetics, which replace damaged tissue with nonliving material (usually a metal alloy) in a form that at least approximates natural function. Examples include dental crowns and bridges, heart valves and stents, and knee and hip replacements. Hip prosthetics consist of a stem that fits into the upper end of the femur and an acetabular cup that fits into the pelvis. These meet through a low-friction polyethylene interface. Typically, conventional mass-production casting or forging processes form the two parts out of Ti and Co–Cr alloys. But because the range of sizes is consequently limited, orthopedic surgeons must modify the upper femoral cavity to accommodate the best-fitting hip stem available. The resulting fit may not be exact, which leads to variable cement gaps

and a weaker implant. This problem has prompted considerable work on adapting additive-manufacturing processes such as EBM to the production of prostheses exactly tailored to the patient's geometry, as determined by CAT or MRI data. Ti and Co—Cr alloys are biocompatible and have more than enough strength to carry the structural loads of a hip joint over the patient's lifetime. Unfortunately, the density and stiffness of these materials are much higher than those of the bone being replaced, so future replacement surgeries are often needed. Again, additive-manufacturing techniques can be used to provide material distributions that match actual bone—that is, a dense structure in the outer region (cortical bone tissue) and a lattice-like internal structure (trabecular region)—leading to weight distribution and flexibility that more nearly match that of an actual hip joint. This is a typical example of the functionally graded material, as discussed in Chapter 12. Both stem and cup components of hip prostheses must integrate with their mating bone structures through tissue ingrowth at their surfaces to ensure long implant lifetime and prevent painful repair operations. EBM produces acetabular cups having an optimized “lacy” surface with deep porosity. The number of successful applications using this method is approaching several thousand. In contrast to the replacement therapies described above, regenerative therapies use porous scaffolds seeded with stem cells and growth factors to provide a platform for the growth of new tissue. After being seeded, the scaffolds are placed in a bioreactor to acclimatize the implant *in vitro* to the temperature and fluid-flow rate it will experience *in vivo*. The scaffold is then placed in the damaged area of the bone, and natural cellular interaction takes place between the scaffold and surrounding sound tissues for a seamless repair.

Additive manufacturing plays a significant role in regenerative medicine because it can generate scaffolds from scan data to produce the precise shape needed to fill damaged areas. It can also generate controlled pore morphologies that provide comfortable attachment points for the seeded cells. Current efforts focus on additive methods for producing bone scaffolds from hydroxyapatite and polymer—ceramic combinations (<http://machinedesign.com/article/additive-manufacturing-for-biomedical-0707>). Additive manufacturing is steadily gaining acceptance for production of critical components in different industries. Production cases usually revolve around parts with complex geometries and sometimes also the use of materials that are difficult or expensive to process with conventional methods. The inherent production challenges of such parts create a drive to look for innovative production methods. In the orthopedic field, such challenges are present in two obvious areas, patient-specific (custom) implants based on CT data and press-fit standard implants with advanced porous materials (<http://www.arcam.com/industry-segments/index.aspx>).

References

- [1] Bessing C, Bergman B. The castability of unalloyed titanium in three different casting machines. *Swed Dent J* 1992;16:109–13.

- [2] Chai TI, Stein RS. Porosity and accuracy of multiple-unit titanium casting. *J Prosthodont* 1995;73:534–41.
- [3] Schädlich-Stubenrauch J, Augthun M, Sahn PR. Untersuchungen zu den mechanischen Eigenschaften und zur Porenbildung von Titan bei verschiedenen Gussverfahren. *Dtsch Zahnäztz Z* 1994;49:774–6.
- [4] Anderson M, Bergman B, Bessing C, Ericsson G, Lundquist P, Nilson H. Clinical results with titanium crowns fabricated with machine duplication and spark erosion. *Acta Odontol Scand* 1989;47:279–86.
- [5] Sjögren G, Andersson M, Bergman M. Laser welding of titanium in dentistry. *Acta Odontol Scand* 1988;46:247–53.
- [6] Russell MM, Andersson M, Dahlmo K, Razzoog ME, Lang BR. A new computer-assisted method for fabrication of crowns and fixed partial dentures. *Quint Int* 1995;26:757–63.
- [7] Mueller HJ, Giuseppetti AA, Waterstratt RM. Phosphate-bonded investment materials for titanium casting. *J Den Res* 1990;69:367 [Abstract No. 2072].
- [8] Dunigan-Miller J. Electrochemical corrosion behavior of commercially pure titanium materials fabricated by different methods in three electrolytes. Indianapolis, IN: Indiana University Master Thesis; 2004.
- [9] Okabe T, Herø H. The use of titanium in dentistry. *Cell Mater* 1995;5:211–30.
- [10] Lautenschlager EP, Monaghan P. Titanium and titanium alloys as dental materials. *Int Dent J* 1993;43:245–53.
- [11] Okabe T, Shimizu H, Woldu M, Brezner M, Carrasco L, Watanabe K. Mechanical properties of titanium cast using yttria face-coating. *THERMEC 2000-Proceedings of International Conference on Processing and manufacturing of Advanced Materials*. vol.117/3, Section A7. Las Vegas; December CDROM, 2000.
- [12] Wang RR, Fenton A. Titanium for prosthetic applications: a review of the literature. *Quint Int* 1996;27:401–8.
- [13] Baltag I, Watanabe K, Kusakari H, Miyakawa O. Internal porosity of cast titanium removable partial dentures: influence of sprue direction on porosity in circumferential clasps of a clinical framework design. *J Prosthet Dent* 2002;88:151–8.
- [14] Cecconi BT, Koeppen RG, Phoenix RD, Cecconi ML. Casting titanium partial denture frameworks: a radiographic evaluation. *J Prosthet Dent* 2002;87:277–80.
- [15] Yoda M, Konno T, Takada Y, Iijima K, Griggs J, Okuno O, et al. Bond strength of binary titanium alloys to porcelain. *Biomaterials* 2001;22:1675–81.
- [16] Okuno O, Hamanaka H. Application of beta titanium alloys in dentistry. *Dent Jpn* 1989;26:101–4.
- [17] Okuno I. New beta-titanium alloys. *Metal* 1990;44:4–9.
- [18] Ida K, Tsustumi S, Togaya M. Titanium and titanium alloys for dental casting. *J Dent Res* 1980;59:985 [Abstract No. 397].
- [19] Taira M, Moser JB, Greener EH. Studies of Ti alloys for dental castings. *Dent Mater* 1989;5:45–50.
- [20] Ita I. Dental casting technique of titanium. *Met Technol* 1985;55:4–9.
- [21] Nakamura S. Ohara's titanium castings for dental use. *Titanium Zirconium* 1986;34:154–6.
- [22] Nakamura S. Casting of titanium for dental use. *Met Technol* 1988;58:16–9.
- [23] Eriksson M, Andersson M, Carlström E. Titanium dental coping prepared by a powder metallurgy method: a preliminary report. *Int J Prosthodont* 2004;17:11–6.
- [24] Stoll R, Okuno O, Ai M, Stachniss V. Titanium casting technique. Possibilities, problems, and hopes. Position report on pure titanium castings. *ZWR* 1991;100:38–42.

- [25] Ida K, Togaya T, Tsutsumi S, Takeuchi M. Effect of magnesia investments in the dental casting of pure titanium and titanium alloy. *Dent Mater J* 1982;1:8–21.
- [26] Mori T, Jean-Louis M, Yabugami M, Togaya T. The effect of investment type on the fit of cast titanium crowns. *Aust Dent J* 1994;39:348–52.
- [27] Okuno O, Yoneyama T, Hamanaka H. Advanced casting of titanium. *Iron Steel* 1990;76:1633–41.
- [28] Koike M, Chai Z, Fujii H, Brezner M, Okabe T. Corrosion behavior of cast titanium with reduced surface reaction layer made by a face-coating method. *Biomaterials* 2003;24:4541–9.
- [29] Miyakawa O, Watanabe K, Okawa S, Nakano S, Kobayashi M. Reaction layers of titanium cast in molds containing spinel. *J Dent Mater* 1995;14:560–8.
- [30] Zhang J, Okazaki M, Takahashi J. Effect of casting methods on surface state of pure titanium casting. *J Dent Mater* 1994;13:221–7.
- [31] Oliveira PCG, Luis Adabo G, Ribeiro RF, Rocha SS. The effect of mold temperatures on castability of CP Ti and Ti-6Al-4V castings into phosphate bonded investment materials. *Dent Mater* 2006;22:1098–102.
- [32] Bauccio ML. Technical note 9: descaling and special surface treatments. In: Boyer R, Welsch G, Collings EW, editors. *Materials properties handbook: titanium alloys*. Materials Park, OH: ASM International; 1994. p. 1080.
- [33] Donachie MJ. *Titanium: a technical guide*. Metals Park, OH: ASM International; 1988. p. 28.
- [34] Cai Z, Bunce N, Nunn M, Okabe T. Porcelain adherence to dental cast CP titanium: effects of surface modifications. *Biomaterials* 2001;22:979–86.
- [35] Walter M, Reppel P, Boning K, Freesmeyer W. Six-year follow-up of titanium and high-gold porcelain-fused-to-metal fixed partial dentures. *J Oral Rehabil* 1999;26:91–6.
- [36] Bergman B, Marklund S, Nilson H, Hedlund S. An intraindividual clinical comparison of 2 metal-ceramic systems. *Int J Prosthodont* 1999;12:444–7.
- [37] Hashimoto H, Kuroiwa A, Wada K, Hibino Y, Kouchi H, Hashimoto T, et al. Reaction product on the surface of titanium castings. *J Dent Mater* 1992;11:603–14.
- [38] Shafer T, Cai Z, Carrasco L, Okabe T. Porcelain bonding to cast titanium made from oxide face-coated patterns. *J Dent Res* 2002;81:A-261 [Abstract No. 2003].
- [39] Nakamura M, Jyohzaki K, Kimura T, Togaya T, Ida K. Ceramic dental molds for the precision casting of titanium and titanium alloys: 1. Relationship between particle size distribution of aggregates and mold expansion. *J Am Ceram Soc* 1990;73:35–8.
- [40] Nakamura S, Komasa Y. Titanium casting procedure using thermal expansion-inhibited investment. Part 3: In the condition of the large colloidal silica particles as mixing liquid. *J Jpn Prosthodont Soc* 1999;38:753–65.
- [41] Ferenczi AM, Demri B, Moritz M, Muster S. Casted titanium for dental applications: an XPS and SEM study. *Biomaterials* 1998;19:1513–5.
- [42] Ott D. Gießen von Titan im Dentallabor (Entwicklung eines Verfahrens). *Metal* 1990;44:366–9.
- [43] Sampath K. The use of technical cost modeling for titanium alloy process selection. *J Metals* 2005;57:25–32.
- [44] Fukui H, Wei Y, Yamada S, Fujishiro Y, Morita A, Niinomi M. Cold crucible levitation melting of biomedical Ti-30 wt%Ta alloy. *Dent Mater J* 2001;20:156–63.
- [45] Elioulo D, Zinelis S, Papadopoulos T. Porosity of cpTi casting with four different casting machines. *J Prosthet Dent* 2004;92:377–81.

- [46] Tokunaga J, Kojima T, Kinuta S, Wakabayashi K, Nakamura T, Yatani H, et al. Larger-area electron beam irradiation for surface polishing of cast titanium. *Dent Mater J* 2009;28:571–7.
- [47] Koike M, Jacobson DJ, Chan KS, Okabe T. Grindability of alpha-case formed on cast titanium. *Dent Mater J* 2009;28:587–94.
- [48] Ohkubo C, Hosoi T, Ford JP, Watanabe I. Effect of surface reaction layer on grindability of cast titanium alloys. *Dent Mater* 2006;22:268–74.
- [49] Iiyama K, Doi H, Hanawa T. Effect of mold temperature on the mechanical durability of titanium casting clasp model. *Dent Mater J* 2009;28:610–9.
- [50] Atwood RC, Lee PD, Curtis RV, Maijer DM. Modeling the investment casting of a titanium crown. *Dent Mater* 2007;23:60–70.
- [51] Turner R. Titanium investment castings. *Adv Mater Proc* 2008;166:35–6.
- [52] Zlatin N, Field M. Procedures and precautions in machining titanium alloys. *Titanium Sci Technol* 1973;1:489–504.
- [53] Ohkubo C, Shimura I, Aoki T, Hanatani S, Hosoi T, Hattori M, et al. Wear resistance of experimental Ti–Cu alloys. *Biomaterials* 2003;24:3377–81.
- [54] Tajima K, Miyawaki A, Nagamatsu Y, Kakigawa H, Kozono Y. Electro-polishing of titanium and its alloys for miller finishing. *J Jpn Dent Mater* 2005;24:406.
- [55] Kyo K, Ohmori H, Okamoto Y. Characteristics of mirror surface grinding of dental nickel-titanium alloy using ELID (electrolytic in-process dressing). *J Jpn Soc Precision Eng* 1998;32:183–7.
- [56] Kalpakjian S. *Manufacturing engineering and technology*. New York, NY: Addison-Wesley Publishing; 1989. pp. 463–64.
- [57] Seman GA. *Practical guide to electro-discharge machining*. 2nd ed. Geneva: Ateliers Des Charmilles SA; 1975 [chapter 2].
- [58] Rubeling G, Hans-Albert K. Spark erosion in dental technology: possibilities and limitations. *Quint Dent Tech* 1984;8:649–57.
- [59] Salinas TJ, Finger IM, Thaler JJ, Clark RS. Spark erosion implant supported overdentures: clinical and laboratory techniques. *Implant Dent* 1992;1:246–51.
- [60] Weber H, Frank G. Spark erosion procedure: a method for extensive combined fixed and removable prosthodontic care. *J Prosth Dent* 1993;69:222–7.
- [61] Jemt T, Linden B. Fixed implant-supported prostheses with welded titanium frameworks. *Int J Periodont Restor Dent* 1992;12:177–83.
- [62] Ntsi A, Muelle WD, Eliades G, Zinelis S. The effect of electro discharge machining (EDM) on the corrosion resistance of dental alloys. *Dent Mater* 2010;26:e236–45.
- [63] Anderson M, Anderson M. Spark erosion. Swedish Patent 8400396-1 1987.
- [64] Anderson M, Oden A. A new all ceramic crown. A dense sintered, high purity alumina coping with porcelain. *Acta Odontol Scand* 1993;51:59–64.
- [65] Maeda Y, Yamada M, Nokubi T, Tsustsumi S, Urabe T. Clinical application of the DCS precedent CAD/CAM system. *Quint Dent Tech* 1996;19:9–20.
- [66] Andersson M, Carlsson L, Persson M, Bergman B. Accuracy of machine milling and spark erosion with a CAD/CAM system. *J Prosthet Dent* 1996;76:187–93.
- [67] Adell R, Lekholm V, Rockler B, Branemark PIA. 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg* 1981;10:387–416.
- [68] Dérand T, Herø H. Bonding strength of porcelain on cast vs wrought titanium. *Scan J Dent Res* 1992;100:184–8.
- [69] Setz J, Diehl J. Gingival reaction on crowns with cast and sintered metal margins: a progressive report. *J Prosthet Dent* 1994;71:442–6.

- [70] van der Zel JM. Ceramic fused to metal restoration with a new CAD/CAM system. *Quint Int* 1993;24:769–78.
- [71] Krishna CG, Prasad YVRK, Birla NC, Rao GS. Hot-deformation mechanisms in near-alpha titanium alloy. *J Metal* 1996;48:56–9.
- [72] Oshida Y. Current trends in research on superplasticity. *J Jpn Soc Plast* 1986;27:357–63.
- [73] Padmanabhan KA, Davies GJ. *Materials research and engineering 2: superplasticity*. New York, NY: Springer-Verlag; 1980.
- [74] Paton NE, Hamilton CH, editors. *Superplastic Forming of Structural Alloys*. The Metallurgical Society of AIME, Conference Proceeding. 21–24, June 1982. San Diego, CA.
- [75] Ghosh AK, Bieler TR, editors. *Superplasticity and superplastic forming 1998*. TMS, Conference Proceeding; 1998.
- [76] Sastry SML, Lederich RL, Mackay TL, Kerr WR. Superplastic forming characterization of titanium alloys. *J Met* 1983;135:48–53.
- [77] Langdon TG, Furukawa M, Horita Z, Nemoto M. Using intense plastic straining for high-strain-rate superplasticity. *J Met* 1998;150:41–5.
- [78] Mishra RS, McFadden SX, Valiev RZ, Mukherjee AK. Deformation mechanisms and tensile superplasticity in nanocrystalline materials. *J Met* 1999;151:37–40.
- [79] Friedrich HE, Winkler P-J. Near-net shape airframe part. *Adv Mater Process* 1991;145:16–22.
- [80] Oshida Y. Transformation plasticity of steels and titanium alloys in compression. Syracuse: NY, Syracuse University Thesis; 1967.
- [81] Ultrafine-grain metals. In: Burke JJ, Weiss V, editors. *Proceedings of the sixth sagamore army materials research conference*, vol. 16. Syracuse, NY: Syracuse University Press; 1970.
- [82] Ultrafine-grain ceramics. In: Burke JJ, Reed NL, Weiss V, editors. *Proceedings of the fifth sagamore army materials research conference*, vol. 15. Syracuse, NY: Syracuse University Press; 1970.
- [83] Ceramics and polymers. In: Burke JJ, Weiss V, editors. *Proceedings twentieth sagamore army materials research conference*, vol. 20. Syracuse, NY: Syracuse University Press; 1975.
- [84] Wakai F, Kodama Y, Sakaguchi S. Superplasticity of hot isostatically pressed hydroxylapatite. *J Am Ceram Soc* 1990;73:457–60.
- [85] Matsusita T, Tsuda T. Superplastic forging of Ti-based alloys and Ni-based alloys. *Materials* 1990;38:130–6.
- [86] Kato M, Murakami H. On the dental application of titanium-based alloy. Part 2: Ceramic die for superplastic forming. *Gov Indust Res Inst* 1990;39:309–17.
- [87] Okuno O, Nakano T, Hamanaka H, Kato I. Diffusion bonding to titanium alloys during superplastic forming. *J Jpn Soc Dental Mater Devices* 1991;10:483–91.
- [88] Wakabayashi N, Ai M. Thickness and accuracy of superplastic Ti-6Al-4V alloy denture frameworks. *Int J Prosthodont* 1996;9:520–6.
- [89] Oshida Y. An application of superplasticity to powder metallurgy. *J Jpn Powder Powder Met* 1975;22:147–53.
- [90] Takase S, Oshida Y. On the solid-state bonding in cast irons using dynamic superplastic phenomena. *Trans Iron Steel Inst Jpn* 1977;17:506–15.
- [91] Mitsuya H, Okada M, Kato I. Superplastic forming of titanium alloy for dental use. *Titanium Zirconium* 1990;37:19–23.
- [92] Klug KL, Ucok I, Gungor MN, Guclu M, Kramer LS, Troy Tack W, et al. The near-net-shape manufacturing of affordable titanium components for the M777 lightweight Howitzer. *J Met* 2004;56:35–42.

- [93] Froes FH, Moshl SJ, Moxson VS, Hebeisen JC, Daz VA. The technologies of titanium powder metallurgy. *J Met* 2004;56:46–8.
- [94] Ning CQ, Zhou Y. On the microstructure of biocomposites sintered from Ti, HA and bioactive glass. *Biomaterials* 2004;25:3379–87.
- [95] Zhao X, Liu X, Ding C. Acid-induced bioactive titania surface. *J Biomed Mater Res* 2005;75A:888–94.
- [96] Cook SD, Thongpreda N, Anderson RC, Haddad RJ. The effect of post-sintering heat treatments on the fatigue properties of porous coated Ti-6Al-4V alloy. *J Biomed Mater Res* 1988;22:287–302.
- [97] Güden M, Celik E, Hizal A, Altindiş M, Cetiner S. Effects of copaction pressure and particle shape on the porosity and compression mechanical properties of sintered Ti6Al4V powder compacts for hard tissue implantation. *J Biomed Mater Res B Appl Biomater* 2008;85:547–55.
- [98] Íşerî U, Özkurt Z, Kazazoğlu E. Shear bond strengths of veneering porcelain to cast, machined and laser-sintered titanium. *Dent Mater J* 2011;30:274–80.
- [99] Sakamoto Y, Asaoka K, Kon M, Matsubara T, Yoshida K. Chemical surface modification of high-strength porous Ti compacts by spark plasma sintering. *J Biomed Mater Eng* 2006;16:83–911.
- [100] Nicula R, Lüthen F, Stir M, Nebe B, Burkel E. Spark plasma sintering synthesis of porous nanocrystalline titanium alloys for biomedical applications. *Biomol Eng* 2007;24:564–7.
- [101] Peter WH, Muth T, Chen W, Yamamoto Y, Jolly B, Stone NA, et al. Titanium sheet fabricated from powder for industrial applications. *J Met* 2012;64:566–71.
- [102] Morgan PED. Superplasticity in ceramics. In: Burke JJ, Reed NL, Weiss V, editors. *Ultrafine-grain ceramics*. Syracuse, NY: Syracuse University Press; 1970. p. 251–71.
- [103] Nonami T, Wakai H. Superplastic bio-ceramics. *Met Technol* 1991;12:36–41.
- [104] Bulger M. Metal injection molding. *Adv Mater Process* 2005;163:39–40.
- [105] Erickson AR, Amaya HE. Recent development in injection molding of P/M parts. In: Aqua EN, editor. *Modern developments in powder metallurgy*. Princeton, NJ: American Powder Metallurgy Institute; 1984. p. 145–55.
- [106] Yamagishi T, Ito M, Kou Y, Obata A, Deguchi T, Hayashi S, et al. Mechanical properties of sintered titanium using metal injection molding. *J Jpn Dent Mater* 1995;14:1–7.
- [107] Scharvogel M, Winkelmueller W. Metal injection molding of titanium for medical and aerospace applications. *J Met* 2011;63:94–6.
- [108] Wiech RE. Method of making inelastically compressible ductile particulate material article and subsequent working thereof. U.S. Patent No.4,445,936 1984.
- [109] Billiet R. Net-shape full density P/M parts by injection molding. *Int J Powder Metallurgy Powder Technol* 1985;21:119–29.
- [110] Wei TS, German RM. Injection molded tungsten heavy alloy. *Int J Powder Metallurgy* 1988;24:327–35.
- [111] Ma LW, Chung CY, Tong YX, Zheng YF. Properties of porous TiNbZr shape memory alloy fabricated by mechanical alloying and hot isostatic pressing. *J Mater Eng Perform* 2011;20:783–6.
- [112] Dahotre NB. Laser surface engineering. *Adv Mater Process* 2002;160:35–9.
- [113] Kopel A, Reitz W. Laser surface treatment. *Adv Mater Process* 1999;159:39–41.
- [114] Singh J. The constitution and microstructure of laser-surface-modified metals. *J Met* 1992;44:8–14.
- [115] Mazumder J. Laser welding. In: Bass M, editor. *Laser materials processing*. North-Holland Publishing; 1983. p. 115–200.

- [116] Bass M, Jau B, Wallace R. Shaping materials with lasers. In: Bass M, editor. Laser materials processing. North-Holland Publishing; 1983. p. 290–336.
- [117] Yamagishi T, Ito M, Fujimura Y. Mechanical properties of laser welds of titanium in dentistry by pulsed Nd:YAG laser apparatus. *J Prosthet Dent* 1993;70:264–73.
- [118] Gordon TE, Smith DL. Laser welding of prostheses—an initial report. *J Prosthet Dent* 1970;24:472–6.
- [119] Huling JS, Clark RE. Comparative distortion in three-unit fixed prostheses joined by laser welding, conventional soldering, or casting in one piece. *J Dent Res* 1977;56:128–34.
- [120] van Benthem H, Munster JV. Korrosionsversuche an Dentallegierungen vor und nach dem Laserschweißen. 1. Hochgoldhaltige Dentallegierungen. *Dtsch Zahnärztl Z* 1985;40:286–9.
- [121] Yamagishi T, Ito M, Masuhara E. Laser-welding of titanium and other dental alloys. Part 1. Mechanical properties of laser welds of titanium by pulsed Nd:YAG laser apparatus. *J Jpn Dent Mater* 1991;10:763–72.
- [122] Yamakura K, Kajima M, Mori K, Yokoyama K, Igarashi T, Onizawa T, et al. Studies on the laser welding in titanium. *J Jpn Soc Oral Implant* 1997;10:420–5.
- [123] Rubenstein JE, Ma T. Comparison of interface relationships between implant components for laser-welded titanium frameworks and standard cast frameworks. *Int J Oral Maxillofac Implants* 1999;14:491–5.
- [124] Roggensack M, Walter MH, Böning KW. Studies on laser- and plasma-welded titanium. *Dent Mater* 1993;9:104–7.
- [125] Suzuki Y, Ohkubo C, Abe M, Hosoi T. Titanium removable partial denture repair using laser welding: a clinical report. *J Prosthet Dent* 2004;91:418–20.
- [126] Berg E, Wanger WC, Davik G, Dootz ER. Mechanical properties of laser-welded cast and wrought titanium. *J Prosthet Dent* 1995;74:250–7.
- [127] Watanabe I, Liu J, Atsuta M. Effects of heat treatment on mechanical strength of laser-welded equi-atomic AuCu-6at%Ga alloy. *J Dent Res* 2001;80:1813–7.
- [128] Iwasaki K, Ohkawa S, Rosca ID, Uo M, Akasaka T, Watari F. Distortion of laser welding titanium plates. *Dent Mater J* 2004;23:593–9.
- [129] Srimanepong V, Yoneyama T, Kobayashi E, Doi H, Hanawa T. Mechanical strength and microstructure of laser-welded Ti-6Al-7Nb alloy castings. *Dent Mater J* 2005;24:541–9.
- [130] Srimanepong V, Yoneyama T, Kobayashi E, Doi H, Hanawa T. Comparative study on torsional, ductility and fracture characteristics of laser-welded $\alpha + \beta$ Ti-6Al-7Nb, CP titanium and Co-C alloy dental castings. *Dent Mater* 2008;24:839–45.
- [131] Shimakura M, Yamada S, Takeuchi M, Miura K, Ikeyama J. Influence of irradiation conditions on the deformation of pure titanium frames in laserwelding. *Dent Mater J* 2009;28:243–7.
- [132] Nuñez-Pantoja JMC, Vaz LG, MAdA Nóbilo, Mesquita MF. Fatigue performance of joints executed in pure titanium structures with several diameters. *Dent Mater J* 2011;3:887–93.
- [133] Abbott DH, Arcella FG. Laser forming titanium components. *Adv Mater Process* 1998;153:29–30.
- [134] Hill MR, DeWald AT, Demma AG, Hackel LA, Chen H-L, Specht RC, et al. Laser peening technology. *Adv Mater Process* 2003;158:65–7.
- [135] Dane CB, Hackel LA, Daly J, Harrison J. Shot peening with lasers. *Adv Mater Process* 1998;153:37–8.

- [136] Hollander DA, von Walter M, Wirtz T, Sellei R, Schmidt-Rohlfing B, Paar O, et al. Structural, mechanical and *in vitro* characterization of individually structured Ti–6Al–4V produced by direct laser forming. *Biomaterials* 2006;27:955–63.
- [137] Xue W, Krismna BV, Bandyopadhyay A, Bose S. Processing and biocompatibility evaluation of laser processed porous titanium. *Acta Biomater* 2007;3:1007–18.
- [138] Narayan RJ, Jin C, Patz T, Doraiswamy A, Modi R, Chrisey DB, et al. Laser processing of advanced biomaterials. *Adv Mater Proc* 2005;April:39–42.
- [139] Miller PR, Aggarwal R, Doraiswamy A, Lin YJ, Lee YS, Narayan RJ. Laser micro-machining for biomedical applications. *J Met* 2009;61:35–40.
- [140] Joya Y, Wang T, Liu Z. Formation and antibacterial activities of nanostructured TiO₂ thin films by sol–gel/laser induced technique. *Int Congr Appl Lasers Electro-Optics* 2011;October(23) [Florida, USA].
- [141] Weigl P, Kasenbacher A, Werelius K. Dental applications. In: Dausinger F, Lichtner F, Lubatschowski H, editors. Femtosecond technology for technical and medical applications. *Topics Appl Phys*. 2004;96:167–87.
- [142] Gamaly EG, Rode AV, Luther-Davis B, Tikhonchuk VT. Ablation of solids by femtosecond lasers: ablation mechanism and ablation thresholds for metals and dielectrics. *Phys Plasmas* 2002;9:949–53.
- [143] Frentzen M, Winkelstraeter C, van Benthem H, Koort HJ. Bearbeitung der Schmelzoberflächen mit gepulster Laserstrahlung. *Dtsch Zahnärztl Z* 1994;49:166–8.
- [144] Draper CW, Poate JM. Laser surface alloying. *Int Metal Rev* 1985;30:85–108.
- [145] Galerie A, Fasasi A, Pons M, Caillet M. Improved high temperature oxidation resistance of Ti-6Al-4V by superficial laser alloying. In: Sudarshan TS, Braza JF, editors. *Surface Modification Technologies*. The Institute of Materials London: UK; 1992. p. 401–11.
- [146] Joya YF, Liu Z, Wang T. Characterization and antibacterial functions of Ag-TiO₂ and W-TiO₂ nanostructured thin films prepared by sol-gel/laser-induced technique. *Appl Phys B* 2009;105:525–36.
- [147] Watanabe I, McBride M, Newton P, Kurtz KS. Laser surface treatment to improve mechanical properties of cast titanium. *Dent Mater* 2009;25:629–33.
- [148] Guo Z, Zhou L, Rong M, Zhu A, Geng H. Bone response to a pure titanium implant surface modified by laser etching and microarc oxidation. *Int J Oral Maxillofac Implants* 2009;24:130–6.
- [149] Balla VK, Banerjee S, Bose S, Bandyopadhyay A. Direct laser processing of a tantalum coating on titanium for bone replacement structures. *Acta Biomater* 2010;6:2329–34.
- [150] Bandyopadhyay A, Balla VK, Roy M, Bose S. Laser surface modification of metallic biomaterials. *J Met* 2011;63:94–9.
- [151] Coelho PG, Giro G, Teixeira HS, Marin C, Witek L, Thompson VP, et al. NRFA. Argon-based atmospheric pressure plasma enhances early bone response to rough titanium surfaces. *J Biomed Mater Res A* 2012;100:1901–6.
- [152] Barnes SJ, Bhatti AR, Steuwer A, Johnson R, Altenkirch J, Whithers PJ. Friction stir welding in HSLA-65 steel: Part 1. Influence of weld speed and tool material on microstructural development. *Metall Mater Trans A* 2012;43:2342–55.
- [153] Miura I, Ida K. *Titanium for dental use*. Tokyo: Quintessence Publishing; 1988. p. 123–31.
- [154] ASM Committee on Titanium and Titanium Alloys. Heat treating of titanium and titanium alloys. *Metals Handbook*; 1981. p. 330–41.

- [155] Banerjee R, Nag S, Stechschulte J, Fraser HL. Strengthening mechanisms in Ti-Nb-Zr-Ta and Ti-Mo-Zr-Fe orthopedic alloys. *Biomaterials* 2004;25:3413–9.
- [156] Franco RL, Chiesa R, de Oliveira PT, Beloti MM, Rosa AL. Bone response to Ca- and P-enriched titanium surface obtained by anodization. *Braz Dent J* 2008;19:15–30.
- [157] Cheng GJ, Ye C. Experiment, thermal simulation, and characterization on transmission laser coating of hydroxyapatite on metal implant. *J Biomed Mater Res A* 2010;92:70–9.
- [158] Liao S, Murugan R, Chan CK, Ramakrishna S. Processing nanoengineered scaffolds through electrospinning and mineralization suitable for biomimetic bone tissue engineering. *J Mech Behav Biomed Mater* 2008;1:252–60.
- [159] Ravichandran R, Ng CCH, Liao S, Pliszka D, Raghunath M, Ramakrishna S, et al. Biomimetic surface modification of titanium surfaces for early cell capture by advanced electrospinning. *Biomed Mater* 2012;7:015001.
- [160] Murr LE, Quinones SA, Gaytn SM, Lopez MI, Rodela A, Martinez EY, et al. Microstructure and mechanical behavior of Ti-6Al-4V produced by rapid-layer manufacturing, for biomedical applications. *J Mech Behav Biomed Mater* 2009;2:20–32.
- [161] Parthasarathy J, Starly B, Raman S, Christensen A. Mechanical evaluation of porous titanium (Ti6Al4V) structures with electron beam melting (EBM). *J Mech Behav Biomed Mater* 2010;3:249–59.
- [162] Harris ID. Additive manufacturing: a transformational advanced manufacturing. *Adv Mater Proc* 2012;170:25–9.

11 Surface Modifications

11.1 Introduction

Surface modifications have been applied to metallic biomaterials in order to improve mechanical, chemical, and physical properties—such as wear resistance, corrosion resistance, biocompatibility, and surface wettability. For enhancing the mechanical retention between two surfaces, one or both surfaces are normally modified to increase effective surface area by a sandblasting, shot-peening, or laser-peening method. High-quality osteointegration means an accelerated healing process of traumatized bone, high stability, and durability of the implants. Using current materials and techniques, a titanium dental implant requires several months to osteointegrate with its adjacent bone. Moreover, the analysis of retrieved titanium implants showed that the bone-to-implant contact (BIC) ratio is far from perfect, averaging 70–80%, with a minimum of 60%, even for successful implants that had lasted for up to 17 years [1], suggesting that the osteointegration has been incomplete for a long period of time. Therefore, much room remains for the improvement of the surface quality of a titanium dental implant (and also orthopedic implants), in terms of the rate and strength of its osteointegration (in other words, survival rate or longevity). Another distinct purpose of surface modification is found on implant surfaces for both dental and orthopedic applications to exhibit biological, mechanical, and morphological compatibilities to receiving vital hard/soft tissue, resulting in promoting osteointegration. Such modifications can provide graded functionality, as will be discussed later, and are generally divided into two categories: surface concave texturing and surface convex texturing. Surface concave textures can be achieved by either material removal by chemical or electrochemical action or mechanical indentations (caused by sandblasting, shot-peening, or laser-peening). Depending on blasting/peening operational conditions (including media size, arc-heights, and coverage), beneficial compressive residual stress can be built at the surface zone. On the other hand, surface convex textures can be achieved by depositing certain types of particles by one of several physical or chemical depositing methods (chemical vapor deposition (CVD), PVD, plasma-spraying, etc.) or solid-state diffusion bonding. If the density and porosity of deposited particles can be appropriately controlled, a porous surface can be achieved, leading to successful bone ingrowth.

As Elias and Oshida et al. [2,3] mentioned, the biological properties of titanium depend on its surface oxide film. Several mechanical and chemical treatments have

been used to modify the surface morphology and properties of titanium dental implants. One possible method of improving dental implant biocompatibility is to increase surface roughness and decrease the contact angle, leading to better wettability and favorable hydrophilicity. The biological properties of dental implants were investigated through *in vivo* and *in vitro* tests. The effects of surface roughness, contact angle, and surface morphology on titanium dental implant removal torque were investigated. Machined dental implants and disks made with commercially pure titanium (CpTi) ASTM grade 4 were submitted to sandblasting treatments, acid-etching, and anodizing. The sample surface morphologies were characterized by scanning electron microscopy (SEM), the surface roughness parameters were quantified using a laser noncontact profilometer, and a contact angle measurement was taken. Dental implants were placed in the tibia of rabbits and removed 12 weeks after the surgery. It was found that (i) acid-etching homogenized the surface roughness parameters, (ii) the anodized surface presented the smallest contact angle; (iii) the *in vivo* test suggested that the surface treatment had a beneficial effect on the implant biocompatibility measured through removal torque, and (iv) the anodized dental implant exhibited the highest removal torque [2]. Hence, it suggests that controlling surface roughness is one of the most important parameters that govern the subsequently occurring osteointegration.

Biological survival, particularly longevity of biological adhesive joints, is often dependent on thin surface films. Surfaces and interfaces behave completely different from bulk properties. The characteristics of a biomaterial surface govern the processes involved in biological response. Surface properties such as surface chemistry, surface energy, and surface morphology may be studied in order to understand the surface region of biomaterials. The surface plays a crucial role in biological interactions for four reasons: (1) the surface of a biomaterial is the only part contacting with the bioenvironment, (2) the surface region of a biomaterial is almost always different in morphology and composition from the bulk, (3) for biomaterials that do not release or leak biologically active or toxic substance, the characteristics of the surface governs the biological response (foreign material vs. host tissue), and (4) some surface properties such as topography affect the mechanical stability of the implant–tissue interface [[4–8], Figure 8.1]. Like the interface, the surface has a certain characteristic thickness, (1) for the case when the interatomic reaction is dominant, such as wetting or adhesion, atoms within a depth of 100 nm (1000 Å) will be important, (2) for the case of the mechanical interaction, such as tribology and surface hardening, since the elasticity due to the surface contact and the plastically deformed layer will be a governing area, the thickness of about 0.1–10 µm will be important, and (3) for the case when mass transfer or corrosion is involved, the effective layer for preventing the diffusion will be within 1–100 µm [4–8]. Such important surfaces can be further modified or altered in a favorable fashion to accommodate, facilitate, or promote more biofunctionality and bioactivity through mechanical, chemical, electrochemical, thermal, or any combination of these methods. Surfaces are the primary place of contact between a biomaterial and its host organism. Typically, prostheses have to fulfill demanding structural and mechanical requirements, yet the material best for those functions

may be bioincompatible. Surface treatment or coating provides a means to overcome that problem, which means both integration within the host physiology and stabilization with respect to corrosion and wear. The adsorption of biomacromolecules is pivotal for biocompatibility. The impossibility of keeping proteins away from most implants means that very careful consideration has to be given to this aspect, and both prevention (for bloodstream implants) and promotion (for bone replacement and repair) occur with equal importance [9].

It should be crucial to understand the interactions between the host bones and the titanium implant in a living body, which occur mostly in the bone–implant interface. Both *in vivo* and *in vitro* studies indicated that surface characterization of implants dominantly controlled such interactions [10]. Such surface characterization should include surface morphology, surface chemistry, and surface energy, which significantly affect the initial bone cell's responses to the implant at the bone–implant interface [11]. The surface energy of a biomaterial is determined by the material's surface charge density and net polarity of the charge. Compared to an electrically neutral surface, a surface with net positive or negative charge may be more hydrophilic [12]. The surface charge of a dental implant is known to be a key factor to promote bone cells' adhesion and early stage bone mineralization in the bone–implant interface. Importance of detailed surface characterization in microscale and nanoscale had been emphasized by several reports [13–16]. In this chapter, taking aforementioned important points into consideration, a variety of surface modifications will be discussed.

11.2 Mechanical Modification

11.2.1 Sandblasting and Surface Texturing

Sandblasting, as well as shot-peening (which will be discussed in the following section), has three purposes: (1) cleaning surface contaminants, (2) roughening surfaces to increase effective surface area,¹ and (3) producing beneficial surface compressive residual stress, depending on the blasting conditions. As a result, such treated surfaces exhibit higher surface energy, indicating higher surface chemical

¹ In order to estimate the increased surface effective area by sandblasting with shot media with an average particle size of 120 μm , 20 μm (1/6 of diameter 120 μm) will be indented, let us assume that the coverage is 100% and effective surface area A^{SP} can be defined as follows by knowing original surface area A° ; Increment in effective surface area = $(A^{\text{SP}} - A^\circ)/A^\circ \times 100$ (%), where

$$\begin{aligned} A^{\text{SP}} &= (\alpha/360) \times 4\pi r^2 \\ \alpha &= 2 \times \cos^{-1} (40/60) = 2 \times 48.2 = 96.4; \text{ and } r = 60 (\mu\text{m}) \\ &\cong 12115^\circ \\ A^\circ &= \pi(d/2)^2 \\ d/2 &= 60 \times \sin(\alpha/2) = 44.7 \\ &\cong 6277^\circ \end{aligned}$$

Then $(A^{\text{SP}} - A^\circ)/A^\circ \times 100$ (%) = $(12115 - 6277)/6277 \times 100 \cong 95\%$.

In fact, the original surface area can be roughly doubled under mild sandblasting operation.

and physical activities, and improving fatigue strength as well as fatigue life. Enhanced bond strength obtained in any possible bonding couples in such dentine bonding system (e.g., porcelain/Ti bonding, or bone/Ti implant) can be generally explained by a favorable result of blasting (causing tons of small indentations on surface) to increase the effective surface area.

Although the recent development of investment materials and casting machines has enabled clinical applications of titanium in dentistry, there remain several problems to be solved. First of all, efficient finishing techniques are required. Titanium is known to be difficult to grind because of its plasticity, stickiness, low heat conductivity, and chemical reactivity at high temperatures [17,18]. Although blasting shows several advantages, there is evidence of adverse effects: (1) surface contamination, depending on the type of blasting media, and (2) distortion of blasted workpiece, depending on the blasting manner and intensity. Miyakawa et al. [19] studied the surface contamination of abraded titanium. Despite low grinding speeds and water cooling, the abraded surfaces were found to be contaminated by abrasive constituent elements. Element analysis and chemical bond state analysis of the contaminants were performed using an electron probe microanalyzer. X-ray diffraction (XRD) of the abraded surface was performed to identify the contaminants. It was reported that (i) the contamination of titanium is related to its reactivity as well as its hardness, (ii) in spite of water cooling and slow-speed abrading, titanium surfaces were obviously contaminated, (iii) contaminant deposits with dimensions ranging from about 10 to 30 μm occurred throughout the surfaces, and (iv) the contaminant of titanium, although related also to the hardness, resulted primarily from a reaction with abrasive materials, and such contamination could negatively influence titanium's resistance to corrosion and its biocompatibility [19].

In order to obtain satisfactory fixation and biofunctionality of biotolerated and bioinert materials, some of the mechanical surface alternations such as threaded surface, grooved surface, pored surface, and roughened surface have been produced that promote tissue and bone ingrowth. But so far, there is no report on suitable roughness of specific metallic biomaterials (see Figure 7.1). In general, on the macroscopic level ($> 10 \mu\text{m}$), roughness will influence the mechanical properties of the interface, the way stresses are distributed and transmitted, the mechanical interlocking of the interface, and the biocompatibility of biomaterials. On a smaller scale, surface roughness in the range from 10 nm to 10 μm may influence the interface biology because it is of the same order in size as cells and large biomolecules. Topographic variations of the order of 10 nm and less may become important because microroughness on this scale length consists of material defects such as grain boundaries, steps, and vacancies, which are known to be active sites for adsorption, and thus may influence the bonding of biomolecules to the implant surface. There is evidence that surface roughness on a micron scale allows cellular adhesion that alters the overall tissue response to biomaterials. Microrough surfaces allow early better adhesion of mineral ions or atoms, biomolecules, and cells, form stronger fixation of bone or connective tissue, result in a thinner tissue-reaction layer with inflammatory cells decreased or absent, and prevent microorganism adhesion and plaque accumulation, when compared with the smooth surfaces [20].

Evaluation/Characterization

Piattelli et al. [21] conducted a histological and histochemical evaluation in rabbits to study the presence of multinucleated giant cells (MGCs) at the interface with machined, sandblasted (with 150 μm alumina media), and plasma-sprayed titanium implants. It was reported that (i) MGCs were not observed around machined and sandblasted titanium surfaces, whereas (ii) MGCs were present at the interface with titanium plasma-sprayed (TPS) implants at 2 weeks and at 2 months, (iii) at 4 and 8 weeks these cells tended to decrease in number, and (iv) an inflammatory infiltrate was not present in connection with the MGCs [21].

The effect of shot-blasting treatment on the cyclic deformation and fracture behavior of CpTi two different microstructures (equiaxed α -phase and acicular martensitic α' -phase) was investigated. Fatigue tests were carried out in artificial saliva at 37°C. Cyclic deformation tests were carried out up to fracture, and fatigue crack nucleation and propagation were analyzed. Residual stresses were determined by means of XRD. It was reported that (i) shot-blasting treatment improves fatigue life in the different microstructures, (ii) the equiaxed phase has improved mechanical properties compared to the acicular one, and (iii) despite the fact that control of the variables of shot blasting is not precise because of the nature of the treatment, it improves the fatigue life by the fact that the initiation site of the fatigue crack changes from the surface of the specimen to the interior of the shot-blasted specimen. This is a consequence of the layer of compressive residual stresses that the treatment generates on titanium surfaces. It was found that, therefore, shot blasting, which is widely used in titanium dental implants in order to favor their osteointegration, can also improve their fatigue resistance [22]. Compressive residual stress can serve as a crack closure, resulting in delaying fatigue crack initiation and, accordingly, its propagation.

It is well known that the osteointegration of the CpTi dental implant is improved when the metal is shot blasted in order to increase its surface roughness. This roughness is colonized by bone, which improves implant fixation. However, shot blasting also changes the chemical composition of the implant surface because some shot particles remain adhered on the metal, causing potential contamination. CpTi surfaces shot blasted with different materials and sizes of shot particles were tested in order to determine their topographical features (surface roughness, real surface area, and the percentage of surface covered by the adhered shot particles) and electrochemical behavior (open circuit potential (OCP), electrochemical impedance spectroscopy (EIS), and cyclic polarization). The results demonstrate that the increased surface area of the material because of the increasing surface roughness is not the only cause of differences found in the electrochemical behavior and corrosion resistance of the blasted CpTi. Among other possible causes, those differences may be attributed to the compressive residual surface stresses induced by shot blasting. All the materials tested have an adequate corrosion and electrochemical behavior in terms of their possible use as dental implant material [23].

The effects of sandblasting media and steam-cleaning treatment after sandblasting were examined on tensile bond strength of porcelain to titanium. The use of the

commercially available silica-coated alumina particles for sandblasting was significantly effective for increasing bond strength than the conventional alumina. It might be due to the increased surface roughness and existence of remaining silica on titanium surface. Additional application of steam cleaning on the titanium surface after sandblasting could make the surface configuration clear in SEM by removing some sandblasted particles loosely embedded in titanium as well as the debris and oily contaminants. The resultant bond strength was significantly improved to reach almost the maximum strength of this porcelain–titanium system regardless of the kind of sandblasting media used, which was confirmed by the observation of the failure mode showing that most of the fracture surface was occupied by cohesive failure in porcelain [24].

Blasting Media

Normally, fine alumina particles ($50\text{ }\mu\text{m Al}_2\text{O}_3$) are recycled within the sandblasting machine. Ceramics such as alumina are brittle in nature; therefore, some portions of recycled alumina might be brittle-fractured. If fractured sandblasting particles are involved in the recycling media, it might result in irregular surfaces, as well as potential contamination. Using fractal dimension analysis [25–27], a sample plate surface was analyzed weekly in terms of topographic changes, as well as chemical analysis of sampled recycled Al_2O_3 particles. It was found that after the accumulated usage time exceeded 30 min, the fractal dimension (D_F) [25] remained at a constant value of about 1.4; prior to that it continuously increased from 1.25 to 1.4. By the electron probe microanalysis on collected blasting particles, unused Al_2O_3 contains 100% Al, whereas used (accumulated usage time was about 2400 s) particles contained Al (83.32 wt%), Ti (5.48 wt%), Ca (1.68 wt%), Ni (1.36 wt%), Mo (1.31 wt%), S (1.02 wt%), Si (0.65 wt%), P (0.55 wt%), Mn (0.49 wt%), K (0.29 wt%), Cl (0.26 wt%), and V (0.08 wt%); this strongly indicated that used alumina powder was heavily contaminated and a high risk for the next material surface to be cross-contaminated. Such contaminants are from previously blasted materials having various chemical compositions and investing materials as well [28]. Tribochemical treatment has been proposed to enhance the bond strength between titanium crown and resin base. Using silica-coated alumina as a blasting media under relatively low pressure, silica layer is expected to remain on the blasted surface so that retention force is enhanced by silane-coupling treatment [29].

Although alumina (Al_2O_3) or silica (SiO_2) particles are most frequently used as a blasting media, there are several different types of powder particles utilized as media. Surface roughness modulates the osteointegration of orthopedic and dental titanium implants. This process may cause the release of cytotoxic silicium or aluminum ions in the peri-implant tissue. To generate a biocompatible roughened titanium (RT) surface, an innovative grid-blasting process using biphasic calcium phosphate (BCP) particles was developed. Ti–6Al–4V disks were either polished, BCP grid-blasted, or left as-machined. BCP grid-blasting created an average surface roughness of $1.57\text{ }\mu\text{m}$ compared to the original machined surface of $0.58\text{ }\mu\text{m}$. X-ray photoelectron spectroscopy (XPS) indicated traces of calcium and phosphorus and relatively

less aluminum on the BCP grid-blasted surface than on the initial titanium specimen. It was reported that (i) SEM observations and measurement of mitochondrial activity (methyl tetrazol sulfate (MTS) assay) showed that osteoblastic MC3T3-E1 cells were viable in contact with the BCP grid-blasted titanium surface, (ii) MC3T3-E1 cells expressed alkaline phosphatase (ALP) activity and conserved their responsiveness to bone morphogenetic protein (BMP2), and (iii) the calcium phosphate grid-blasting technique increased the roughness of titanium implants and provided a noncytotoxic surface with regard to mouse osteoblasts [30].

Surface modification of Ti-based metals is an important issue in improving the bone cell responses and bone-implant integration. Blasting Ti with granules (mostly alumina) is commonly used to prepare a clean surface and provide a level of roughness. Glass granules with a bioactive composition were used as the blasting source to improve the surface bioactivity and biocompatibility of a Ti substrate. Bioactive glass (BAG) particles ($70\text{SiO}_2 \cdot 25\text{CaO} \cdot 5\text{P}_2\text{O}_5$) were prepared using a sol-gel method. Ti disk was blasted with glass particles using a dental blasting unit (BG-Ti). A Ti disk blasted with commercial spherical-shaped glass (G-Ti) and a disk without blasting (Ti) were also prepared for comparison. The blasted Ti contained a large number of glass particles after the blasting process. The surface roughness of the samples in ascending order was $\text{G-Ti} > \text{BG-Ti} > \text{Ti}$. Murine-derived preosteoblasts (MC3T3-E1) were seeded on the samples, and the cell growth, differentiation, and mineralization behaviors were observed. It was reported that (i) the osteoblastic cells attached well and spread actively over all the sample groups with extensive cytoskeletal processes, (ii) the level of cell growth on the BG-Ti showed a continual increase with culturing up to 7 days, showing good cell viability; however, there was no significant difference with respect to the G-Ti and Ti groups and (iii), in particular, the ALP activity of the cells was significantly higher on the BG-Ti than on the other groups after culturing for 14 days. It was also found that the mineralization behavior of the cells, as assessed by Alizarin S Red, was superior on the BG-Ti to that observed on the other groups after culturing for 14 and 28 days. It was concluded that the blasting of Ti with a BAG composition is considered beneficial for producing substrates with enhanced osteogenic potential [31].

Recently, it was reported that sandblasting using alumina as a media caused a remarkable distortion on a Co-Cr alloy and a noble alloy [32,33]. It was estimated that the stress causing the deflection exceeded the yield strength of tested materials. It was also suggested that the sandblasting should be done using the lowest air pressure, duration of blasting period, and particle size alumina in order to minimize distortion of crowns and frameworks. To measure distortion, Co-Cr alloy plates (25 mm long, 5 mm wide, 0.7 mm thick) were sandblasted with Al_2O_3 of 125 μm . Distortion was determined as the deflection of the plates as a distance of 20 mm from the surface. It was reported that (i) the mean deflections varied between 0.37 and 1.72 mm, and (ii) deflection increased by an increase in duration of the blasting, pressure, particle size, and by a decrease in plate thickness [32].

There are several evidences of surface contamination due to mechanical abrasive actions. As a metallographic preparation, the surface needs to be mechanically

polished with a metallographic paper (which is normally SiC-adhered paper) under running water [34], Oshida Y. Unpublished data, 2012]. It is worth mentioning here that the polishing paper should be changed between different types of materials, and, particularly when a dissimilar metal-couple is used for galvanic corrosion tests, such a couple should not be polished prior to corrosion testing because both materials could become cross-contaminated [Oshida Y. Unpublished data, 2012]. Hence, there are attempts to use TiO₂ powder for blasting onto titanium material surfaces. It was reported that titanium surfaces were sandblasted using TiO₂ powder (particle size ranging from 45, to 45–63, to 63–90 µm) to produce the different surface textures prior to fibroblast cell attachment [35].

Blasting + Other Treatment

There are numerous studies on the effects of multiple treatments, namely sandblasting (with alumina, hydroxyapatite (HA), or titania powder as blasting media) followed by acid- or alkali-treatment. Using a rabbit femur model, histomorphological and histomorphometrical *in vivo* responses were evaluated to three variations in the resorbable blasting media (RBM) surface processing [36]. Screw root form implants with 3.75 mm in diameter by 8 mm in length presenting four surfaces: (1) alumina-blasted/acid-etched (AB/AE), (2) bioresorbable ceramic blasted (tricalcium phosphate, TCP), (3) TCP + acid-etching, and (4) AB/AE + TCP were characterized by SEM and atomic force microscopy (AFM). The implants were placed at the distal femur of 8 New Zealand rabbits, remaining for 2 weeks *in vivo*. After sacrifice, the implants were nondecalfified and processed to 30 µm thickness slides for histomorphology and BIC determination. SEM and AFM revealed that all surfaces presented rough textures and that calcium-phosphate particles were observed at the TCP group surface. Histologic evaluation showed intimate interaction between newly formed woven bone and all implant surfaces, demonstrating that all surfaces were biocompatible and osteoconductive. It was also reported that (i) significant differences in BIC were observed between the AB/AE and the AB/AE + TCP, and intermediate values observed for the TCP and TCP + acid surfaces, and (ii) all surfaces were osteoconductive and biocompatible [36].

Using a beagle model, the *in vivo* performance of two nanothickness ion beam–assisted depositions (IBAD) of bioceramic coatings on implants were physicochemically characterized and evaluated [37]. Alumina-blasted/acid-etched (AB/AE) Ti–6Al–4V implants were subjected to two different IBAD depositions (IBAD I and IBAD II), which were physicochemically characterized by SEM, energy-dispersive spectroscopy (EDS), XPS, XPS + ion-beam milling (depth profiling), XRD, AFM, and time-of-flight secondary ion mass spectrometer (ToF-SIMS). A beagle dog tibia model was utilized for histomorphometric and biomechanical (torque) comparison between AB/AE, IBAD I, IBAD II, and plasma-sprayed hydroxyapatite (PSHA) coated implants that remained *in vivo* for 3 and 5 weeks. It was found that (i) the coatings were characterized as amorphous Ca–P with high Ca/P stoichiometries with thicknesses of an order of magnitude difference (IBAD I: 30–50 nm and IBAD II: 300–500 nm) and (ii) the

histomorphometric and biomechanical testing results showed that the 300–500 nm thickness deposition (IBAD II) and PSHA positively modulated bone healing at early implantation times [37].

Titanium surfaces submitted to different treatments were characterized and the response of osteoblasts derived from human alveolar bone to these surfaces was evaluated [38]. Five different surfaces were evaluated: ground (G), ground and chemical etched (G1-HF for 60 s), sandblasted (SB- Al_2O_3 particles 65 μm), sandblasted and acid etched (SBA1-HF for 60 s and SBA2-HF for 13 s). Surface morphology was evaluated under SEM and roughness parameters by contact scanning instrument. The presence of Al_2O_3 was detected by EDS and the amount calculated by digital analyses. Osteoblasts were cultured on these surfaces and it was evaluated in terms of cell adhesion, proliferation, and viability, ALP activity, total protein content, and matrix mineralization formation. It was reported that (i) Al_2O_3 residues were detected on sandblasted and SBA2 surfaces, (ii) only matrix mineralization formation was affected by different surface treatments, being increased on rough surface (SBA1) and reduced on surface with high amount of Al_2O_3 residues (sandblasted); it was concluded that high concentration of residual Al_2O_3 negatively interfere with the process of matrix mineralization formation in contact with Ti implant surfaces [38].

In the rabbit tibia, CpTi implants, which were sandblasted with 25 μm Al_2O_3 and TiO_2 particles, were inserted in the rabbit tibia for 12 weeks. Even though the amount of Al on the implant surface was higher than for the Al_2O_3 -blasted implants compared to implants not blasted with Al_2O_3 , any negative effects of the Al element were not detected [39], which is in contrast to those reported by Johansson et al. [40], who reported that Al release from Ti–6Al–4V implants was found to coincide with a poorer bone-to-implant over a 3-month period. It is possible that the lack of differences between TiO_2 -blasted and the Al_2O_3 -blasted implants depends on lower surface concentrations of toxic Al ions than those reported by Johansson et al. [40]. Wang [41] investigated the effects of various surface modifications on porcelain bond strengths. Such modifications included Al_2O_3 blasting, TiO_2 blasting, HNO_3 + HF + H_2O treatment, H_2O_2 treatment, and preoxidation in air at 600°C for 10 min. Ti-porcelain couples were subjected to three-point bending tests. It was concluded that TiO_2 air abrasion showed the highest bond strength, which was significantly different from other surface treatments.

The effect of dilute HCl as a sodium removal treatment of grit-blasted/NaOH/heat-treated CpTi implants was evaluated on the *in vitro* bioactivity and the *in vivo* interface shear resistance at different healing periods [42]. Cylindrical implants were machined from CpTi bars. Half of the implants were blasted by Al_2O_3 particles followed by NaOH/heat treatment. The other half received similar treatment except dilute HCl was additionally used as a sodium removal treatment. Implant surface topography was characterized by AFM before and after immersion in simulated body fluid (SBF) for 3 and 7 days. The implants' resistance to interfacial shear force was evaluated at 2-, 4-, and 8-week implantation periods in experimental rabbits. It was found that (i) sodium removal treatment significantly increased surface roughness, valley fluid retention index, and surface area before and after

immersion in SBF; however, it significantly decreased core fluid retention index, (ii) calcium and phosphorus containing surface deposits, of larger surface area, were precipitated on implants that received the sodium removal treatment after 3 and 7 days in SBF, and (iii) the implant–bone interface resistance to shear force was significantly increased at 2 weeks healing period after the use of the sodium removal treatment. It was, therefore, suggested that (i) the sodium removal treatment showed to be effective in improving the early bone–implant interface resistance to shear force and (ii) topographical changes, after dilute HCl etching, seem to contribute to the different *in vitro* and/or *in vivo* responses observed [42].

The surface chemistry, hydration capacity, topography, and roughness of the root part of a hydrophilic SBA titanium dental implant were investigated [43]. Implants, after water rinsing and ultrasonication in water, were subjected to XPS (X-ray photoelectron spectroscopy) elemental and binding state analyses. It was reported that (i) as-received implant demonstrated higher $[-OH]/O^{2-}$ ratio than the acid-etched implant, (ii) EDS microanalysis documented higher O, Na, Cl, and lower Ti content in as-received implant, (iii) more $-OH$ contributions were probed on the acid-etched implant in comparison with as-received implant, and (iv) Ti–O peaks assigned to anatase, rutile, and amorphous phases were found in both implant groups, suggesting the increased surface hydroxylated titanium content and the greater spatial and functional roughness parameters, may explain the enhanced biological activity [43].

Titanium implants are most commonly used for bone augmentation and replacement due to their favorable osteointegration properties. Here, hyperhydrophilic SBA titanium surfaces were produced by alkali treatment and their responses to partially heparinized whole human blood were analyzed. Blood clot formation, platelet activation, and activation of the complement system were analyzed, revealing that exposure time between blood and the material surface is crucial as increasing exposure time results in higher amount of activated platelets, more blood clots formed, and stronger complement activation. In contrast, the number of macrophages/monocytes found on alkali-treated surfaces was significantly reduced as compared to untreated SBA Ti surfaces. Interestingly, modified SBA Ti surfaces are very different blood clots formed on their surfaces when being compared to untreated surfaces. On untreated Ti surfaces, blood clots remain thin (below 15 mm), patchy, and nonstructured, lacking large fibrin fiber networks, whereas blood clots on differentiated surfaces assemble in an organized and layered architecture of more than 30 mm thickness. Close to the material surface most nucleated cells adhere; above, large amounts of nonnucleated platelets remain entrapped within a dense fibrin fiber network providing a continuous cover of the entire surface. Based on these findings, it was indicated that, combined with findings of previous *in vivo* studies demonstrating that alkali-treated SBA Ti surfaces perform better in terms of osseointegration, a continuous and structured layer of blood components on the blood-facing surface supports later tissue integration of an endosseous implant [44].

The effects of the addition of oxide structure with submicron-scale porous morphology were evaluated on the peri-implant bone response around Ti implants with

microroughened surfaces [45]. HA-blasted Ti implants with (experimental) and without (control) a porous oxide structure produced by chemical treatment were investigated in a rabbit femur model. Surface characterizations and *in vivo* bone response at 4 and 8 weeks after implantation were compared. It was found that (i) the experimental implants had a submicron-scale porous surface structure consisting of anatase and rutile phases, and the original surface roughness values produced by blasting were preserved, (ii) the histomorphometric evaluation demonstrated statistically significant increased BIC for experimental implants, both in the three best consecutive threads and all threads at 4 weeks, and (iii) the porous Ti oxide surface enhanced peri-implant bone formation around the Ti implants with microroughened surfaces at the early healing stage. Based on these results, it was concluded that the addition of crystalline Ti oxide surface with submicron-sized porous morphology produced by chemical treatment may be an effective approach for enhancing the osteointegration of Ti implants with microroughened surfaces by increasing early bone–implant contact [45].

Laser treatment has become a popular method for resolving peri-implantitis, but the full range of its effects on implant surfaces is unknown. Hence, the influence of different clinically applicable Er:YAG, CO₂, and diode laser parameters was analyzed on titanium surfaces that were either polished or sandblasted, large-grit, and acid-etched. Six polished and six SBA titanium disks were irradiated at nine different power settings with Er:YAG, CO₂, or diode lasers. Each disk was irradiated on six circular areas of 5 mm in diameter with the same specific laser setting for 10 s. It was found that the CO₂ and diode laser did not cause any visible surface alterations on either the polished or SBA disks and, in contrast, both polished and SBA disks showed surface alterations when irradiated with the pulsed Er:YAG laser. It was, therefore, concluded that (i) in contrast to continuous-wave diode and CO₂ laser irradiation, pulsed Er:YAG laser irradiation caused distinct alterations with power settings beyond 300 mJ/10 Hz on the SBA surface and 500 mJ/10 Hz on the polished surface and (ii) it is only safe to use the Er:YAG laser for implant surface irradiation with settings no higher than 300 or 500 mJ/10 Hz [46].

The cellular activities of MG63 osteoblast-like cells on modified titanium surfaces were studied. MG63 osteoblast-like cells were cultured on titanium disks with turned, RBM-treated or anodized surfaces. The surfaces of commercially available implants of Osstem (Osstem Implant) were reproduced for the titanium disks. The morphology of cells cultured on these disks was examined using SEM. Specimens were also evaluated with an initial cell adhesion assay to compare initial adhesion, with an MTS assay to compare the proliferation ability and with an ALP assay to compare the differentiation ability. It was reported that (i) attached cells with more defined lamellipodia and flattened morphology were observed on the anodized and RBM surfaces than on the turned surfaces, (ii) titanium surfaces were all oxidized as titanium oxide and polluted by carbon determinants, and (iii) anodized titanium surfaces exhibited calcium and phosphorus peaks. Initial cell attachment activity, cell proliferation activity, and ALP activity were higher on the anodized surfaces than on the other surfaces, and (iv) cell differentiation on the anodized surfaces at culture day 10 was significantly higher than on the other

surfaces. It was, hence, concluded that surface treatment by anodization may improve initial attachment of cells, proliferation ability, and differentiation activity, which play important roles in providing better osteointegration of implants; this suggests that more rapid and stronger osteointegration of implants may make it possible to offer the best anchorage and shorten the healing time required prior to functional loading [47].

11.2.2 Shot-Peening and Laser-Peening

Shot-peening (which is a similar process to sandblasting, but has more controlled peening power, intensity, and direction) is a cold working process in which the surface of a part is bombarded with small spherical media called shot. Each piece of shot striking the material acts as a tiny hammer, imparting to the surface small indentations or dimples. In order for the dimple to be created, the surface fibers of the material must be yielded in tension. Below the surface, the fibers try to restore the surface to its original shape, thereby producing below the dimple a hemisphere of cold-worked material highly stressed in compression. Overlapping dimples (which are sometimes called forged dimples) develop an even layer of metal in residual compressive stress. It is well known that cracks will not initiate or propagate in a compressively stressed zone due to a tendency of a crack-closure phenomenon. Since nearly all fatigue and stress corrosion cracking failures originate at the surface of a part, compressive stresses induced by shot-peening provide considerable increases in part life, since advancing crack-opening is suppressed by preexisting compressive residual stress. The maximum compressive residual stress produced at or under the surface of a part by shot-peening is at least as great as half the yield strength of the material being peened. Many materials will also increase in surface hardness due to the cold working effect of shot-peening [48–50]. Both compressive stresses and cold working effects are used in the application of shot-peening in forming metal parts called “shot forming” [49].

Oshida investigated the compressive residual stress distribution in depth underneath the surface of Ti–6Al–4V alloy using the XRD. It was found that the compressive residual stress at the surface was -50 MPa, followed by the maximum compressive residual stress of -80 MPa at $20\text{ }\mu\text{m}$ below the surface. Then, the compressive residual stress starts to decrease to show almost zero stress at about $50\text{ }\mu\text{m}$ underneath the surface in a depth profile curve of residual stress distribution [Oshida Y. Unpublished report, 2012]. It was also shown that shot-peening resulted in better bonding strengths between titanium substrate and porcelain than sandblasting [Oshida Y. Unpublished data, 2012].

The laser-peening technology is recently developed, claiming a noncontact, no-media, and contamination-free peening method. Before treatment, the workpiece is covered with a protective ablative layer (paint or tape) and a thin layer of water. High-intensity ($5\text{--}15\text{ GW/cm}^2$) nanosecond pulses ($10\text{--}30\text{ ns}$) of laser light beam ($3\text{--}5\text{ mm}$ width) striking the ablative layer generate a short-lived plasma which causes a shock wave to travel into the workpiece. The shock wave induces compressive residual stress that penetrates beneath the surface and strengthens the

workpiece [50–53], resulting in improvements in fatigue life and retarding the occurrence of stress corrosion cracking. Cho et al. [54] laser-treated CpTi screws and inserted in right tibia metaphysics of white rabbits for 8 weeks. It was reported that (i) SEM of laser-treated implants demonstrated a deep and regular honeycomb pattern with small pores and (ii) eight weeks after implantation, the removal torque was 23.58 N-cm for control machined and 62.57 N-cm for laser-treated implants. Gaggl et al. [55] reported that (i) surfaces of laser-treated Ti implants showed a high purity with enough roughness for good osteointegration and (ii) the laser-treated Ti had regular patterns of micropore with interval of 10–12 μm , diameter of 25 μm , and depth of 20 μm [55].

At the end of this section, it is necessary to summarize various techniques to measure and characterize the surface roughness. They include that (1) surface roughness can be measured using a profilometer with sharp-edged stylus, which is a contact method, (2) AFM can provide noncontact surface topography from which the surface roughness can be indirectly measured, and (3) fractal dimension analysis can be used to present the surface roughness in non-Euclidian dimension [25,28]. Recently, Hansson et al. [56] employed computer simulations to measure surface roughness. The lateral resolution was defined as the pixel size of a profiling system. A surface roughness was simulated by a trigonometric function with random periodicity and amplitude. The function was divided into an array of pixels simulating the pixels of the profiling system. The mean height value for each pixel was used to calculate the surface roughness parameters. It was found that the accuracy of all the surface roughness parameters investigated decreased with increasing pixel size. This tendency was most pronounced for mean slope and developed length ratio, amounting to about 80% of their true values for a pixel size of 20% of the true mean high-spot spacing. It was concluded that the lateral resolution of an instrument/method severely compromises the precision of surface roughness parameters, which are measured for roughness features with a mean high-spot spacing less than five times the lateral resolution [56].

11.3 Chemical, Electrochemical, Thermal, and Physical Modifications

There are several experimental results on chemical, electrochemical, thermal, and combinations of these with regard to altering the Ti surface to facilitate better surface chemical, mechanical, and biological reactions. Since it has been proven that moderately rough surfaces outperform the turned surfaces, recent research has focused on further modifications that could possibly increase the bioactivity of the implant. Thus, some of the state-of-the-art research has shifted to chemically modified moderately rough surfaces, which have been indicated to generate synergistic effects. Furthermore, the surface energy is another important factor involved in the regulation of osteogenesis. It has been said that depending on the surface energy, the surface state can be either hydrophilic or hydrophobic. The energy state of the implant depends on the type of biomaterials, the handling

during manufacturing, the mode of cleaning, sterilization, and, needless to say, the handling of the implant during the surgical procedure. In general, when the surface is positively charged, the surface becomes hydrophilic and some of the plasma proteins essential for the initial stereogenic interactions adsorb to such hydrophilic surfaces. It has been suggested that the charge of the implant surface can be altered by oxidation, by chemical and topological modification, and by plasma treatment.

11.3.1 Chemical and Electrochemical Treatment

Endo [57] treated NiTi in 30% HNO_3 , heated at 400°C for 0.75 h, and HNO_3 treatment, followed by boiling in water for 6–14 h. The variously treated NiTi surfaces were tested for dissolution resistance in bovine serum. It was found that (i) those stems thermally treated were found to have significantly lower metal ion release due to stable rutile oxide (TiO_2) formation, (ii) human plasma fibronectin (an adhesive protein) was covalently immobilized onto an alkylaminosilane derivate of NiTi substrate with glutaraldehyde, and (iii) the XPS spectra suggested that gamma-aminopropyltriethoxysilane (γ -APS) was bonded to the surface through metallosiloxane bonds ($\text{Ti}-\text{O}-\text{Si}$) formed via a condensation reaction between the silanol end of γ -APS and the surface of the hydroxyl group, with a highly cross-linked siloxane network formed after heat treatment of the silanized surface at 100°C . Based on these findings, it was concluded that human plasma fibronectin was immobilized at the surface, and significantly promoted fibroblast spreading, suggesting that this chemical modification offers an effective means of controlling metal–cell interactions [57]. In a study done by Browne et al. [58], hip replacement stems manufactured from the Ti–6Al–4V alloy were surface-treated and tested for dissolution resistance in bovine serum. Specimens were decreased in 1,2-dichloroethane vapor and surface-treated in one of four ways: (1) 35% nitric acid for 10 min—typical commercial treatment, (2) 35% nitric acid for 16 h and rinsed in distilled water, (3) thermal heating in a furnace for 0.75 h at 400°C , and (4) 35% nitric acid, then aged in boiling distilled water in a silica beaker for various times—6, 8, 10, and 14 h. It was found that thermal treatment and aging of the surface oxide encourages the formation of dense rutile structure. This is effective in reducing metal ion dissolution (up to 80%), particularly in the early stages of implantation where the stem surface is equilibrating with its surroundings. This benefit is further enhanced on rough surfaces with an increased surface area. It was, therefore, concluded that (i) the thermal treatment and aging of the surface oxides are important with respect to cementless and porous implants and (ii) such treatments could be incorporated in commercial manufacturing procedures and reduce the risk of metal dissolution being a contributory factor toward revision surgery [58].

MacDonald et al. [59] investigated the microstructure, chemical composition, and wettability of thermally, and chemically modified Ti–6Al–4V disks, and correlated the results with the degree of adsorption between the radiolabeled fibronectin and Ti–6Al–4V alloy surface and subsequent adhesion of osteoblast-like cells.

It was found that (i) heating either in pure oxygen or atmosphere resulted in an enrichment of Al and V within the surface oxide, (ii) heating (in pure oxygen or atmosphere) and hydrogen peroxide treatment, both followed by butanol treatment, resulted in a reduction in content of V, but not in Al, (iii) heating (oxygen/atm) or hydrogen peroxide treatment resulted in a thicker oxide layer and a more hydrophilic surface when compared with chemically passivated controls (in 40% NHO_3); however, the posttreatment with butanol resulted in a less hydrophilic surface than heating or hydrogen peroxide treatment alone, and (iv) the greatest increases in the adsorption of radiolabeled fibronectin following treatment were observed with hydrogen peroxide/butanol-treated samples followed by hydrogen peroxide/butanol and heat/butanol, although binding was only increased by 20–40% compared to untreated control. These experiments with radiolabeled fibronectin indicated that enhanced adsorption to the glycoprotein was more highly correlated with changes in chemical composition, reflected in V content and decrease in the V/Al ratio, than with changes in wettability. Based on these findings, it was concluded that an increase in the absolute content of Al and/or V, and/or in the Al/V ratio is correlated with an increase in the fibronectin-promoted adhesion of an osteoblast-like cell line [59].

Titanium (Ti) has been widely used as an implant material due to the excellent biocompatibility and corrosion resistance of its oxide surface. Biomaterials must be sterile before implantation, but the effects of sterilization on their surface properties have been less well studied. The effects of cleaning and sterilization on surface characteristics were biodetermined using contaminated and pure Ti substrata first manufactured to present two different surface structures: pretreated titanium (PT, $R_a = 0.4 \mu\text{m}$) (i.e., surfaces that were not modified by sandblasting and/or acid-etching); (SBA, $R_a = 3.4 \mu\text{m}$). Previously cultured cells and associated extracellular matrix (ECM) were removed from all biocontaminated specimens by cleaning in a sonicator bath with a sequential acetone $\rightarrow$ isopropanol $\rightarrow$ ethanol $\rightarrow$ distilled water protocol. Cleaned specimens were sterilized with autoclave, gamma irradiation, oxygen plasma, or ultraviolet (UV) light. XPS, contact angle measurements, profilometry, and SEM were used to examine surface chemical components, hydrophilicity, roughness, and morphology, respectively. It was found that (i) cleaning and sterilization affected hydrophobicity and roughness, (ii) these modified surface properties affected osteogenic differentiation of human MG63 osteoblast-like cells, and (iii) autoclaved SBA surfaces lost the characteristic increase in osteoblast differentiation seen on starting SBA surfaces, which was correlated with altered surface wettability and roughness. It was indicated that re-cleaned and re-sterilized Ti implant surfaces cannot be considered the same as the first surfaces in terms of surface properties and cell responses. Therefore, it was concluded that the recycle of Ti implants after re-sterilization may not result in the same tissue responses as found with never-before-implanted specimens [60].

The etching behavior of titanium in concentrated sulfuric acid was characterized. CpTi plate was etched in 48% H_2SO_4 at RT -90°C for 0.25–8 h. It was reported that (i) the surface roughness of CpTi increased with the acid temperature and etching time, (ii) the surface roughness was strongly related to the weight loss, (iii) the

weight loss increased drastically with the acid temperature after an initial period, which shortened with increasing acid temperature, and (iv) the apparent activation energy for the dissolution of CpTi in H_2SO_4 was derived as 67.8 kJ/mol; indicating that the etching with concentrated sulfuric acid is an effective way to modify the surface of titanium for biological applications [61].

The effects of acid-etched titanium on the biological responses of osteoblast-like MC3T3-E1 cells were investigated [62]. Four types of treatments (polishing, sandblasting, concentrated H_2SO_4 etching, and concentrated H_2SO_4 etching with vacuum firing) were carried out on the surfaces of CpTi disks. MC3T3-E1 cells were then cultured on the treated CpTi surfaces. Through surface roughness measurement and SEM analysis, it was found that the acid-etched surfaces showed higher roughness values than the sandblasted ones. SEM analysis showed that the cells on the disks treated with acid-etching and acid-etching with vacuum firing spread as well as the sandblasted ones. There were no significant differences in cell proliferation and collagen production on CpTi among the four different surface treatments. Based on the results of this study, it was concluded that etching with concentrated sulfuric acid was a simple and effective way to roughen the surface of titanium without compromising its biocompatibility [62].

The influence of surface treatments of CpTi samples on *in vitro* bioactivity was studied [63]. CpTi sheets were submitted to three different surface treatments, including, for all samples, etching with a $\text{HCl}/\text{H}_2\text{SO}_4$ solution. Part of each etched sample was further submitted either to anodic oxidation by using a H_3PO_4 solution or to thermal oxidation. Treated and nontreated samples were analyzed by using SEM, profilometry, and XPS. The *in vitro* assessment was carried out through the immersion of samples in SBF. It was shown that, after up to 7 days of exposure, a calcium phosphate layer precipitated on only one sample submitted to at least one of the three treatments used; this is in good agreement with Ca content and XPS analysis, in which remarkable effects of surface modifications on Ti samples are highlighted. These results suggest that suitable surface treatments may improve *in vitro* titanium bioactivity in a SBF solution at 37°C [63].

It has recently been reported that controlled chemical oxidation of titanium with sulfuric acid (H_2SO_4)/hydrogen peroxide (H_2O_2) significantly influences the early stages of *in vitro* osteogenesis. It was evaluated whether this chemical treatment can also influence *in vivo* bone formation. Ti implants were etched with $\text{H}_2\text{SO}_4/\text{H}_2\text{O}_2$ for 4 h at room temperature. Mandibular premolars were extracted in eight dogs and, after 3 months, three treated and three untreated implants were placed in each animal. At 3 and 8 weeks postimplantation, the animals were sacrificed, and the implants with surrounding bone were harvested, fixed with formaldehyde, and processed for embedding in LR White. Sections of bone with the implants were prepared, stained with Stevenel's blue and Alizarin red, and analyzed histomorphometrically for percentage of BIC, percentage of mineralized bone area between threads (BABT), and percentage of mineralized bone area within the mirror area (BAMA). It was reported that (i) treated implants exhibited significantly more BIC than control, untreated ones both at 3 (68.1% vs. 27.9%) and 8 weeks (73.5% vs. 14.7%) postimplantation; with no difference in the BABT and BAMA, and

(ii) histological analysis confirmed that, in most cases, new bone in contact with the implant formed in a direction away from it. It was then indicated that a controlled chemical oxidation of Ti implants significantly enhances contact osteogenesis and suggest that this treatment may be beneficial for early loading of implants [64].

Rohanizadeh et al. [65] investigated methods of preparing different types of titanium oxide (TiO_2) and their effects on apatite (AP) deposition and adhesion on titanium surfaces. CpTi disks were subjected to the following treatments: (1) heat treatment at 750°C ; (2) oxidation in H_2O_2 solution followed by heat treatment; (3) dipping in rutile/gelatin slurry; and (4) dipping in anatase/gelatin slurry. Surface-treated Ti disks were immersed in a supersaturated calcium phosphate solution to allow AP deposition. It was shown that (i) the percentage of area covered by deposited AP was highest in sample disks which were dipped in an anatase/gelatin slurry, compared to the other groups, (ii) AP deposited on Ti disks pretreated in H_2O_2 solution demonstrated the highest adhesion to the titanium substrate, and (iii) the surface treatment method affects the type of TiO_2 layer formed (anatase or rutile) and affects AP deposition and adhesion on the Ti surface [65].

The treatment of peri-implantitis, which causes tissue deterioration surrounding osseointegrated implants, involves surface decontamination and cleaning. However, chemical cleaning agents may alter the structure of implant surfaces. CpTi (grade IV) machined titanium disks were treated with 3% H_2O_2 (for 5 min), saturated citric acid (for 1 min) or chlorhexidine gel (for 5 min). Human epithelial cell attachment (24-h observation) and proliferation (72-h observation) were investigated via dimethylthiazolyl-diphenyltetrazolium bromide (MTT) and bicinchoninic acid protein content assays. It was reported that (i) AFM revealed no significant difference in roughness of the three treated surfaces, (ii) XPS confirmed the constant presence of typical surface elements and an intact TiO_2 layer on each surface, and (iii) XPS peaks after chlorhexidine gel treatment demonstrated C—O and/or C=O bond formation, due to chlorhexidine digluconate infiltrating the surface. MTT and BCA assays indicated similar epithelial cell attachments in the three groups; epithelial cell proliferation was significantly higher after H_2O_2 than after chlorhexidine gel treatment (not shown by BCA assays) [66].

The efficacy of four different fluoride etchants in titanium bonding was studied [67]. The etchants were aqueous solutions of 5 wt% sodium fluoride (NaF), ammonium fluoride (NH_4F), sodium hydrogen fluoride (NaHF), and ammonium hydrogen fluoride (NH_4HF). Cast specimens of CpTi were air-abraded with alumina, etched for 30 s, and then primed with a phosphate primer. An acrylic rod was bonded to the specimen with a tri-*n*-butylborane-initiated self-curing luting agent. Shear bond strengths were determined before and after 10,000 thermocycles. It was found that (i) regarding prethermocycling bond strength, there were no significant differences among the etchants, (ii) after thermocycling, there was a decrease in bond strength for all groups, (iii) nonetheless, the bond strengths of NaHF and NH_4HF were significantly higher than those of NaF, NH_4F , and nonetched control, and (iv) in terms of bonding durability between resin and titanium, it was significantly improved when the titanium surface was microscopically roughened with alumina blasting and etching using NaHF or NH_4HF [67].

The properties of the TiO_2 layer on titanium implant surfaces are decisive for good contact with the surrounding tissue. The oxide properties can be deliberately changed by, for example, chemical etching, ion incorporation, or anodization. Impedance spectroscopy was used to study the semi-conducting properties of the naturally formed oxide for different pretreatment of the surface. A turned surface was used as a reference and both physical (blasting) and chemical (hydrofluoric acid-etching) treatments were investigated. The hydrofluoric acid-etching of the blasted surface results in an oxide film with even higher conductivity. Indication of the defect oxide structure for fluoride-treated samples was also seen when analyzing the TiO^+/Ti^+ ratio. The lowest value of this ratio was obtained for the HF-etched sample, indicating a less stoichiometric oxide compared to the other surfaces. This is a result of incorporation of fluoride ions in the oxide, as proven by adsorption studies on a TiO_2 suspension. The pullout forces data on the rabbit model depend primarily on surface roughness but the contribution from the hydrofluoric acid-etching might be explained by fluoride ion incorporation and the resulting increase in oxide conductivity [68].

Fluoride-modification of dental titanium (Ti) implants is used to improve peri-implant bone growth and BIC and adhesion strength. In this study, the surface topography, chemistry, and biocompatibility of polished Ti surfaces treated with hydrofluoric acid solution (HF) were studied. Murine osteoblasts (MC3T3-E1) were cultured on the different groups of Ti surfaces. Surfaces treated with HF had higher roughness, lower cytotoxicity level, and better biocompatibility than controls. For short treatment times (40 and 90 s), fluorine was detected only within the first 5 nm of the surface layer, whereas longer treatment time (120 and 150 s) caused fluoride ions to penetrate deeper. These results suggest that submerging Ti implants in a weak HF solution promotes the time-dependent specific surface changes that are linked to the improved biocompatibility of these surfaces [69].

Surfaces treated with fluoride are smoother than sandblasted surfaces, but fluoride-treated surfaces showed higher calcium–phosphorous binding capacity, which could indicate an increased ability of the surface to react with calcified tissues and promote integration between bone and implant. Accordingly, in the study by Ellingsen et al. [70], the *in vitro* tests have shown that titanium fluoride treatments have a greater capacity for the nucleation of phosphate crystals than sandblasted Ti implants. *In vivo* fluoride ion-modified implants have generally proven superior to sandblasted surfaces in terms of osteointegration, ultimately increasing the removal torques [70].

It is known that fluoride ions have osteopromoting capacity leading to increased calcification of the bone. Titanium fluoride is reported to form a stable layer on enamel surfaces consisting of titanium that shares the oxygen atoms of phosphate on the surface of HA. Ellingsen et al. [71] investigated as to whether a similar or a reverse reaction would take place on fluoride pretreated titanium after implantation in bone. Threaded TiO_2 -blasted titanium implants were preconditioned with fluoride. The implants were implanted into the tibia of Chinchilla rabbits and allowed to heal for 2 months before the animals were sacrificed. The strength of the bonding between the implants and bones was tested by removing the implants

from the bones with an electronic removal torque gauge. It was reported that (i) the fluoride-conditioned titanium implants had a significantly increased retention in bone (69.5 N-cm) compared to nontreated blasted implants (56.0 N-cm) and smooth surface implants (17.2 N-cm), and (ii) the histological evaluation revealed that new bones formed on the surface of the test implants, as well as in the marrow or cancellous regions, which was not observed in the control groups, suggesting that fluoride conditioning of titanium has an osteopromoting effect after implantation [71]. Furthermore, push-out tests of fluoridated and control Ti implants placed in rabbits for up to 8 weeks were conducted [72]. It was found that the fluoridated implants sustained greater push-out forces than the controls, and substantial bone adhesion was observed in fluoridated implants, whereas the controls always failed at the interface between the bone and foreign materials. In other rabbit tests by Ellingsen et al. [70], it was reported that the fluoridated, blasted implants showed a significantly higher removal torque than the blasted test implant, again indicative of a bioactive reaction of fluoridated Ti implants. Johansson et al. [73] also reported significantly greater bone contact to fluoride-modified titanium implants at 1 and 3 months of follow-up, despite the fact that the blasted controls were moderately roughened.

The bone response to RT implants treated with hydrofluoric acid/nitric acid (HF/HNO₃) solution was studied. Implants were treated with HF/HNO₃ solution (test implants) or without HF/HNO₃ solution (control implants). Forty-five test and 45 control implants were inserted into both tibiae of 15 rabbits. After 2, 4, and 8 weeks *in situ*, tibiae were retrieved and prepared for removal torque testing and histomorphometric evaluation. It was reported that (i) mechanical tests showed that mean removal torque values for the test implants were higher than those of the control implants after 8 weeks (33.1 N-cm vs. 25.7 N-cm), (ii) histomorphometric analysis showed that the bone area (BA) in the threads of the cortical bone region was significantly higher for test implants (81.99% and 86.38%) than for control implants (75.33% and 81.62%) after 4 and 8 weeks of healing, respectively, and (iii) the BIC rate in the cortical region was higher for test implants than for control implants after 8 weeks *in situ* (79.56% vs. 68.45%). It was then concluded that the treatment with HF/HNO₃ solution promotes bone formation and osteointegration after 4 and 8 weeks of bone healing in the rabbit tibia model [74].

Early bone ingrowth secures long-term fixation of primary implants inserted without cement. Implant surfaces roughened with a texture on the micrometer scale are known to be osseoconductive. The bone formation at the surface of acid-etched implants modified on the microscale was evaluated. Implants with a nonparticulate texture made by chemical milling (hydrofluoric acid, nitric acid) (control) were compared with implants that had a dual acid-etched (DAE) (hydrofluoric acid, hydrochloric acid) microtexture surface superimposed on the primary chemically milled texture. An experimental joint replacement model with cylindrical titanium implants (Ti-6Al-4V) was used and implants were inserted, paired, and press-fitted in cancellous tibia metaphyseal bones of eight canines for 4 weeks and evaluated by histomorphometric quantification. It was reported that (i) a significant twofold median increase was seen for bone ingrowth on the acid-etched surface

(median, 36.1%) compared to the control (18.4%), and (ii) the percentage of fibrous tissue at the implant surface and adjacent bone was significantly less for dual acid textured implants compared with control implants, suggesting that secondary roughening of titanium alloy implant surface by DAE increases bone formation at the implant–bone interface [75].

Krozer et al. [76] investigated the possible influence of an amino-alcohol solution on machined Ti surface properties. Screw-shaped CpTi implants and CpTi studs were used. They were rinsed (1) in running deionized water for 2 min, (2) NaCl solution for 2 min followed by deionized water washing, and (3) rinsed in 5% H₂O₂ for 2 min followed by deionized water washing, and rinsed in deionized water for 2 min. The amino-alcohol solution was supplied to the sample surfaces, and four methods were used in order to remove the adsorbed alcohol molecules. It was shown that (i) rinsing in water, saline solution, and 5% H₂O₂ did not remove the amino-alcohol from the surface; however, (ii) exposure to ozone produced by using a commercial mercury lamp in ambient air resulted in complete removal of the adsorbed amino-alcohol, and (iii) the presence of such a film most likely prevents reintegration to occur at the implant–tissue interface *in vivo* [76]. In a study done by Rupp et al. [77], CpTi was first blasted with 354–500 μm large grits, followed by (1) HCl/HF/HNO₃ etching, (2) HCl/H₂SO₄ etching, (3) HCl/H₂SO₄/HF/oxalic acid + neutralized, and (4) HCl/H₂SO₄/HF/oxalic acid + oxidized. It was reported that the Ti modifications, which shift very suddenly from a hydrophobic (high-surface contact angle) to a hydrophilic (low-surface contact angle) state, adsorbed the highest amount of immunologically assayed fibronectin, suggesting that microtexturing greatly influenced both the dynamic wettability of Ti implant surfaces during the initial host contact and the initial biological response of plasma protein adsorption [77].

Surface energy and hydrophilicity of implant surfaces have been known to play an important role in subsequent cellular responses on the implant surface. The effects of biomimetic deposition of anodized surfaces on surface wettability, surface energy, and osteoblast responses were evaluated. Ti disks with two different surface topographies (machined and anodized) were immersed in Hanks' balanced salt solution (HBSS) and modified SBF solution for 2 weeks at physiologic conditions at 37°C. SEM observation and EDS microanalysis showed the deposition of calcium phosphate (Ca-P) onto anodized Ti surfaces immersed in modified SBF. Surface energy, surface wettability, and osteoblast responses, including cell attachment capacity, cell proliferation rate, and cell differentiation level, significantly increased on anodized Ti surfaces immersed in modified SBF. The effects of biomimetic deposition with modified SBF on physicochemical surface characteristics and cell biological responses were greater on anodized surfaces than on machined surfaces. These results indicate that biomimetic deposition with effective SBF may enhance the interaction between anodized Ti surfaces and their biological environment, consequently improving bone healing of dental Ti implants [78].

To combine the advantages of different electrolytes in anodic oxidation, pure titanium samples were anodized in CH₃COOH electrolyte according to a novel

anodizing treatment regime and then in H_2SO_4 electrolyte in potential static mode. The *in vitro* bioactivity of the as-prepared titanium samples was evaluated by SBF test. In addition, MG63 osteoblast-like cells were cultured on surfaces of the as-prepared titanium samples to evaluate osteoblast adhesion ability. It was found that the titanium samples after the two-step anodization treatment were covered by titania layers of anatase and/or rutile with several micrometers thickness and presented a multilevel porous surface morphology consisting of interlaced grooves about $20\text{ }\mu\text{m}$ wide overlaid with submicron scale pores. The SBF test results showed that the crystal titania layers prepared at appropriate conditions were able to induce AP forming in 7 days, indicating that the abundance of surface Ti—OH groups and (101)-oriented rutile structure both played important roles in *in vitro* bioactivity of titania layers. It was also reported that (i) the cell experiment results showed that the macroscopic grooves could effectively promote osteoblast adhesion and growth and submicron scale pores might be beneficial to osteoblast adhesion, and (ii) the two-step anodization treatment might be a promising candidate for surface modification of titanium implants [79].

Titanium and its alloys have good biocompatibility with body cells and tissues and are widely used for implant applications. However, clinical procedures place more stringent and tough requirements on the titanium surface, necessitating artificial surface treatments [80]. Among the many methods of titanium surface modification, electrochemical techniques are simple. By anodic oxidation it is possible to obtain the desired roughness, porosity, and chemical composition of the oxide. Anodic oxidation at high voltages can improve the crystallinity of the oxide. The chief advantage of this technique is doping of the coating of the bath constituents, and incorporation of these elements improves the properties of the oxide. These coatings require a postsintering treatment to improve the coating properties. Cathodic deposition is another type of electrochemical method in which HA is formed *in situ* from an electrolyte containing calcium and phosphate ions. It is also possible to alter structure and/or chemistry of the obtained deposit. Nano-grained HA has higher surface energy and greater biological activity and therefore emphasis is being laid to produce these coatings by cathodic deposition [80].

11.3.2 Chemical + Thermal

Yang et al. [81] investigated the effect of $\text{H}_2\text{O}_2/\text{HCl}$ heat treatment on peri-implant bone formation *in vivo*, using 20 Ti—6Al—4V implants and 30 Ti—6Al—4V disks. The implants and disks were separated into two groups: a sandblasted and DAE group (control group) and a sandblasted, DAE, and $\text{H}_2\text{O}_2/\text{HCl}$ heat-treated group (test group). Surface morphology, roughness, and crystal structure of the disks were analyzed by field-emission SEM, AFM, and low-angle XRD. The implants were inserted into the femurs of 10 adult white rabbits. Animals were injected with fluorescent bone labels at 1, 5, and 7 weeks following surgery to monitor progress of bone formation. Animals were euthanized 8 weeks postsurgery, and block

biopsies were prepared for histologic and histometric analysis. It was found that (i) microscopic evaluation showed the surfaces were quite irregular for both techniques; however, the test surface demonstrated consistently smaller surface irregularities, (ii) the differences in surface roughness values were significant, and (iii) new bone was formed on both implant surfaces. The BIC ratios were as follows: (i) test implants demonstrated 7.13% more BIC and 15.42% more BIC for three consecutive threads than control implants, and (ii) test implants demonstrated 37.04% more BA 500 μm outside of implant threads and 51.97% more BA within three consecutive threads than control implants. It was concluded that implants heat-treated with $\text{H}_2\text{O}_2/\text{HCl}$ solution enhanced peri-implant bone formation [81].

The effects of anatase-structured titania surface on the response of osteoblast-like cells was studied. Three kinds of titanium (Ti) disks were prepared: the polished Ti (PT), the RT formed by sandblasting and acid-etching, and the anatase-coated roughened Ti (ART) formed on the RT via $\text{H}_2\text{O}_2/\text{HCl}$ solution treatment followed by heating at 400°C. The surface topography of Ti disks was observed under a scanning electron microscope. MC3T3-E1 cells were cultured on the Ti disks. Cell morphology was observed by fluorescence microscopy. Cell adhesion and proliferation were assessed by MTT testing. To evaluate the cell differentiation on RT and ART, the expressions of core-binding factor α , osterix, bone sialoprotein (BSP), collagen type I, osteocalcin (OC), and ALP-2 were measured by real-time reverse transcriptase polymerase chain reaction (RT-PCR). It was reported that (i) the three kinds of Ti disks had distinct surface topographic characteristics, (ii) the cells on the ART more rapidly displayed well-defined stress fibers and numerous processes and pseudopodi than the cells on the PT and RT, and (iii) cell proliferation did not differ between groups after 1–5 days of culture. In addition, ART generally enhanced the osteogenic gene expression in a time-dependent manner compared with RT. It was also mentioned that (i) an anatase-structured titania promotes initial adhesion and spreading of osteoblast-like cells, but does not influence cell proliferation and (ii) anatase could also enhance cell differentiation by enhancing osteogenic gene expression [82].

Surface chemistry of dental implant plays an important role in osteointegration. Heat treatment might alter surface chemistry and result in different biological response. Zhang et al. [83] investigated the roles of heat treatment of $\text{H}_2\text{O}_2/\text{HCl}$ -treated Ti implants in cell attachment, proliferation, and osteoblastic differentiation. Sandblasted, DAE, and $\text{H}_2\text{O}_2/\text{HCl}$ heat-treated disks were set as the control group, and sandblasted, DAE, $\text{H}_2\text{O}_2/\text{HCl}$ -treated disks were the test group. MC3T3-E1 cells were seeded on these two groups' disks for 3 h to 14 days, and then cell attachment, cell proliferation, and cell differentiation were evaluated. It was found that (i) scanning electron microscope analysis revealed that the titanium disks in the two groups shared the same surface topography, while XRD examination showed an anatase layer in the control group and titanium hydride diffractions in the test group, (ii) the cell attachment of the test group was equivalent to that of the control group, and (iii) cell proliferation was slightly stimulated at all time points in the control group, but the ALP activity and OC production increased significantly in the test group

compared with those in the control group at every time point investigated. It was concluded that surface chemistry played an important role in cell response, and a $\text{H}_2\text{O}_2/\text{HCl}$ -etched titanium surface without subsequent heat treatment might improve osteointegration response [83].

11.3.3 Alkali + Thermal

A porous Ti–18Nb–4Sn alloy was prepared by powder metallurgy. To enhance the bioactivity of the alloy surface, alkali-heat treatment was used to modify the surface. The bioactivity of the pretreated alloy sample was investigated using a bio-mimetic process by soaking the sample into SBF. It was reported that (i) the elastic modulus and plateau stress of the porous Ti–18Nb–4Sn alloy decrease with decreasing relative density, (ii) the mechanical properties of the porous alloy can be tailored to match those of human bone, (iii) after soaking in SBF for 7 days, a HA layer formed on the surface of the pretreated porous Ti–18Nb–4Sn alloy, and (iv) the pretreated porous Ti–18Nb–4Sn alloy therefore has the potential to be a bioactive implant material [84].

In vitro studies of Ti–6Al–7Nb and Ti–5Al–2Nb–1Ta alloys were carried out by treating the specimens with 10 M NaOH at 60°C for 24 h and subsequently heat-treated at 600°C for 1 h. After the alkali and heat treatments, and on subsequent soaking in SBF, the morphological and compositional changes on the surface of the specimens were examined using a scanning electron microscope with an energy-dispersive electron probe X-ray analyzer attached. The results revealed a dense and uniform bone-like AP layer on the surface of treated substrates immersed in SBF solution. *In vivo* studies were carried out in rats to evaluate osteoconduction of Ti–6Al–7Nb and Ti–5Al–2Nb–1Ta alloy surfaces after alkali and heat treatments compared with untreated titanium alloys as the control. It was found that, histologically, direct bone contact with the implant surface was significantly higher in the alkali heat-treated implants than the untreated titanium implants [85].

11.3.4 Thermal and Physical

Most thermal or physical surface treatment can be found in plasma treatments or oxidation. Li et al. [86] modified the surface of CpTi (grade II) implants by micro-arc oxidation (MAO), operated under voltage ranging from 190, 230, 270, 350, 450 to 600 V to form a porous layer. It was found that (i) with increasing voltage, the roughness (from 0.3 to 2.5 μm) and thickness (from 1 to 15 μm) of the film increased, and (ii) the TiO_2 phase changed from anatase to rutile, supporting what was discussed in Chapter 4. The MAO was carried out in an aqueous electrolyte with calcium acetate monohydrate and calcium glycerophosphate in deionized water. During the MAO, it was found that (i) Ca and P ions were incorporated into the oxide layer, (ii) the *in vitro* cell responses were also dependent on the oxidation condition, and (iii) with increasing voltage, the ALP activity increased, while the cell proliferation rate decreased. Preliminary *in vivo* tests of the MAO-treated specimens on rabbits showed a considerable improvement in their osseointegration

capacity as compared to the unmodified CpTi implant [86]. Surface modification of titanium was investigated by means of hydrothermal treatment with a maximum pressure of 6.3 MPa (at 280°C) in CaO solution or water to improve bioactivity and biocompatibility. As a result, calcium titanate was formed on the titanium surface. Moreover, titanium oxide and titanium hydroxide layers on the surface increased as temperature and pressure increased. The surface-modified titanium was also immersed in a SBF to estimate its bioactivity. Needle-like AP precipitation was observed on all hydrothermal-treated titanium surfaces after immersion in SBF for 4 weeks. In particular, the AP precipitation of titanium treated with 6.3 MPa in CaO solution was clearer and larger in amount than those of all other hydrothermal-treated specimens. Further, the amount of precipitate corresponded to the thickness of the surface-modified layer and the amount of calcium in the surface layer. The results suggested that surface modification of titanium with high-pressure hydrothermal treatment seemed to improve bioactivity and biocompatibility [87]. The surface bioactivity of titanium was investigated after water and hydrogen plasma immersion ion implantation (PI^3) by Xie et al. [88]. PI^3 method excels in the surface treatment of components possessing a complicated shape such as medical implants. In addition, water and hydrogen PI^3 has been extensively studied as a method to fabricate silicon-on-insulator substrates in the semiconductor industry, and so it is relatively straightforward to transfer the technology to the biomedical field. Water and hydrogen were plasma-implanted into titanium sequentially. It was found that (i) after incubation in SBFs for cytocompatibility evaluation *in vitro*, bone-like HA was found to precipitate on the ($\text{H}_2\text{O} + \text{H}_2$) implanted samples, while no AP was found on titanium samples plasma implanted with water or hydrogen alone, and (ii) human osteoblast cells were cultured on the ($\text{H}_2\text{O} + \text{H}_2$)-implanted titanium surface and they exhibited good adhesion and growth. It was therefore suggested that PI^3 is a practical means to improve the surface bioactivity and cytocompatibility of medical implants made of titanium [88].

Changes in the surface of CpTi can determine the functional response of cells, and is therefore a critical factor for the success of the implant. However, the genotoxicity of titanium surfaces has been poorly studied. Tavares et al. [89] evaluated the genotoxic potential of a new titanium surface developed by plasma treatment using argon-ion bombardment and compare it with an untreated titanium surface. Comet assay, analysis of chromosomal aberrations (CAs), and cytokinesis block micronucleus assay were carried out, using CHO-K1 (Chinese hamster ovary) cells grown on both titanium surfaces. It was reported that (i) the untreated titanium surface caused a significant increase in percent tail moment, in the number of cells with CAs, tetraploidy, micronucleus frequency, and other nuclear alterations when compared with the negative control and with the plasma-treated titanium surface, and (ii) this difference may be attributed to increased surface roughness and changes in titanium oxide layer thickness [89].

Gil et al. [90] studied the influence of laser surface modification treatments on mechanical and electrochemical behavior in Ti and Ti–6Al–4V implants. For

each metal, different samples were laser modified. Microstructural changes produced by this treatment were observed: (a) the melting zone with small grain sizes and martensitic structures in aforementioned metals, and (b) the heat-affected zone (HAZ) with alpha phase in CpTi with bigger grain sizes and Widmanstatten structure in Ti–6Al–4V. Positive tensile residual stress was determined by means of X-ray analysis in the zones marked by laser. Furthermore, corrosion behavior was studied in a SBF at 37°C. It was found that (i) pitting was observed in different zones near the HAZ, (ii) the corrosion resistance decreased in the laser treated samples, and (iii) residual stresses and the martensitic microstructures favored the decrease of the corrosion-fatigue life by around 20% in both metals under physiological conditions [90].

11.3.5 UV Treatment

Osteoblast attachment on irradiated titanium disks was investigated since osteoblast attachment on a titanium surface is necessary to achieve new bone formation and osseointegration. Machined, HA-coated, sandblasted, and TPS surfaces were irradiated with either a carbon dioxide (CO₂) or an Er,Cr:YSGG laser. A control group of nonirradiated disks was also examined. Osteoblast cultures were cultivated on the titanium disks and examined with SEM. It was found that (i) osteoblasts could be grown on all of the surfaces, and (ii) pseudopodia and a spread of cells that demonstrated maturation were observed on the laser irradiated titanium disks, concluding that laser irradiation of titanium surfaces may promote osteoblast attachment and further bone formation [91]. Titanium alloys (Ti) are the preferred material for orthopedic applications. However, very often, these metallic implants loosen over a long period and mandate revision surgery. For implant success, osteoblasts must adhere to the implant surface and deposit a mineralized ECM. UV-killed *Staphylococcus aureus* as a novel osteoconductive coating for Ti surfaces was used. The interaction of *S. aureus* with osteoblasts activates growth factor-related pathways that potentiate osteogenesis. Although UV-killed *S. aureus* cells retain their bone-adhesive ability, they do not stimulate significant immune modulator expression. All of the abovementioned properties were utilized for a novel implant coating so as to promote osteoblast recruitment and subsequent cell functions on the bone–implant interface. Samayaji et al. [92] studied osteoblast adhesion, proliferation, and mineralized ECM synthesis on Ti surfaces coated with fibronectin with and without UV-killed bacteria. It was reported that (i) osteoblast adhesion was enhanced on Ti alloy surfaces coated with bacteria compared to uncoated surfaces, while cell proliferation was sustained comparably on both surfaces, and (ii) osteoblast markers such as collagen, OC, ALP activity, and mineralized nodule formation were increased on Ti alloy coated with bacteria compared to uncoated surfaces [92]. Ueno et al. [93] determined whether UV light treatment

of titanium implants could enhance osteointegration to sufficiently overcome the negative aspects of shorter implants in a rat femur model. Acid-etched miniature titanium implants with lengths of 2 mm (longer implants) and 1.2 mm (shorter implants) were prepared. Some of these implants were treated with UV light for 48 h prior to surgery. The strength of osteointegration generated by these implants was evaluated using a biomechanical implant push-in test in a rat model. Peri-implant osteogenesis was examined by SEM for tissue morphology and EDS for elemental composition. It was reported that (i) push-in test values for the longer implants were 80% and 100% greater than those of the shorter implants at weeks 4 and 8 of healing, respectively, (ii) UV treatment of the shorter implants significantly increased their push-in value, resulting in a 100% higher value than untreated longer implants at week 2 and a push-in value that was equivalent to that of the untreated longer implants at weeks 4 and 8, (iii) scanning electron micrographs and EDS examinations after push-in testing revealed that the UV-treated implant surfaces were covered more extensively by bone or tissue remnants containing calcium and phosphorous than the untreated surfaces, and (iv) the titanium surfaces were converted from hydrophobic to superhydrophilic status after UV treatment, although the cause–result relationship between the acquired superhydrophilicity and biologic effects remained unclear. Based on these results, it was concluded that UV light pretreatment substantially enhanced the osseointegration capacity of acid-etched titanium implants and the deficiencies of osteointegration in implants with a 40% shorter length were overcome by UV treatment in the rat model using miniature implants [93]. The effect of UV irradiation was studied on shear bond strength between a titanium and a segmented polyurethane (SPU) composite through γ -mercapto propyl trimethoxysilane (γ -MPS). The shear bond strength of Ti/SPU interface of Ti–SPU composite under varying conditions of UV irradiation was evaluated by a shear bond test. The glass transition temperatures of SPU with and without UV irradiation were also determined using differential scanning calorimetry. It was found that the shear bond strength of Ti/SPU interface increased with UV irradiation. However, excessive UV irradiation decreased the shear bond strength of the Ti/SPU interface. Glass transition temperature was found to increase during 40–60 s of UV irradiation. In terms of durability after immersion in water at 37°C for 30 days, shear bond strength was found to improve with UV irradiation. It was, then, concluded that UV irradiation to a Ti–SPU composite was clearly one of the means to improve the shear bond strength of a Ti/SPU interface [94].

Titanium dioxide (TiO_2), a photocatalyst, is known to decompose various organic compounds under UV illumination by generating various radicals, which is useful for killing bacteria. The photocatalytic bactericidal effects of variously treated titanium surfaces on *Streptococcus sanguinis* SL1 were evaluated. Specimens were fabricated from CpTi (grade IV), 10 mm in diameter and 2 mm in thickness. Three different surfaces were prepared: anodized (AO) at 270 V, heat-treated (HT), and machined (MA). Surface analysis was performed using a confocal laser scanning microscope, SEM, and thin-film X-ray diffractometry.

The antibacterial activities were assessed by comparing adhesion and survival rates of *S. sanguinis* on various surfaces under UV illumination. It was reported that (i) the AO surface was rougher than the HT and MA surfaces, (ii) the AO surface showed TiO₂ peaks of anatase structure, while the HT surface showed TiO₂ peaks of rutile structure in X-ray diffractometry, (iii) HT and AO surfaces showed significantly decreased bacterial adhesion under UV illumination (AO and HT > control, AO > MA), and (iv) bacterial adhesion decreased more significantly with extended UV illumination time. It was concluded that the photoinduced bactericidal efficacy of TiO₂ films is dependent on their surface characteristics [95].

11.4 Coating

The coating layer is not only required to exhibit an expected function, depending on its original specific aims but it is also important to notice that the coating layer is only functional if it adheres well to the metal substrate and if it is strong enough to transfer all loads. Coated substrate possesses at least two layers and one intermediate interface. If such a couple is subjected to stressing, although the strain field should be assumed to be a continuum, the stress field of the couple exhibits a discrete one due to differences in modulus of elasticity (MOE). This discrete stress field results in interfacial stress, and if the interfacial stress is higher than the bonding strength, the couple can be debonded or delaminated, causing the structural integrity to no longer be maintained. Micro- or nanoscale surface roughness enhances osteoblast differentiation on titanium substrates and increases BIC *in vivo*. However, the low surface wettability induced by surface roughness can retard initial interactions with the physiological environment. Chemical modifications of Ti surfaces (pretreated (PT), $R_a \leq 0.3 \mu\text{m}$; SBA, $R_a \geq 3.0 \mu\text{m}$) was examined in order to modify surface hydrophilicity. Coating layers of polyelectrolytes was designed so that they did not alter the surface microstructure but increased the surface ionic character, including chitosan (CHI), poly(L-glutamic acid) (PGA), and poly(L-lysine) (PLL). Ti disks were cleaned and sterilized. Surface chemical composition, roughness, wettability, and morphology of surfaces before and after polyelectrolyte coating were examined by XPS, contact mode profilometry, contact angle measurement, and SEM. It was reported that (i) high-resolution XPS spectra data validated the formation of polyelectrolyte layers on top of the Ti surface, (ii) the surface coverage of the polyelectrolyte adsorbed on Ti surfaces was evaluated with the pertinent SEM images and XPS peak intensity as a function of polyelectrolyte adsorption time on the Ti surface, (iii) PLL was coated in a uniform thin layer on the PT surface. CHI and PGA were coated evenly on PT, albeit in an incomplete monolayer, (iv) CHI, PGA, and PLL were coated on the SBA surface with complete coverage, and (v) the selected polyelectrolytes enhanced surface wettability without modifying surface roughness. It was, therefore, concluded that these chemically modified surfaces on implant devices can contribute to the enhancement of osteoblast differentiation [96].

11.4.1 Carbon, Glass, and Ceramics Coating

The surface of Ti–6Al–4V has been modified by ion beam mixing a thin C film by Demri et al. [97]. XPS analysis showed that after mixing, the surface film consists essentially of a Ti compound containing (Ti, O, and C) TiO_2 , Ti, and C. The composition of the surface-modified film determined by Rutherford backscattering spectrometry is approximately $\text{Ti}_{0.5}\text{O}_{0.3}\text{C}_{0.2}$ and its thickness is about 200 μm . It was also reported that after 3 months' immersion in a SBF, the growth of calcium phosphate species containing both HPO_4^- and H_2PO_4^- (probably CaHPO_4 and $\text{Ca}(\text{PO}_4)_2$) has been observed [97]. The corrosion resistance and other surface and biological properties of NiTi were enhanced using carbon PI^3 and deposition (PI^3). Poon et al. [98] mentioned that either an ion-mixed amorphous carbon coating fabricated by PI^3 and deposition or direct carbon PI^3 can drastically improve the corrosion resistance and block the out-diffusion on Ni from the metal. The tribological tests showed that the treated surfaces are mechanically more superior and cytotoxicity tests revealed that both sets of plasma-treated samples favored adhesion and proliferation of osteoblasts [98]. With regard to potential toxicity of Ni, this is one method of preventing or shielding the Ni element from diffusing out from NiTi surface. There is another way to achieve a similar outcome: selectively leaching out Ni from the NiTi surface layer by chemically etching the NiTi surface in mixed acid aqueous solution of $\text{HF} + \text{HNO}_3 + \text{H}_2\text{O}$ (1:1:3 by volume) [99].

BAG is a bioactive material with a high potential as implant material. Reactive plasma-spraying produces an economically feasible BAG-coating for Ti–6Al–4V oral implants. It was shown that (i) the coating withstands, without any damage, an externally generated tensile stress of 47 MPa and (ii) adhesion testing after 2 months of *in vitro* reaction in a SBF showed that coating adhesion strength decreased by 10%, but the implant was still adequate for load-bearing applications [100].

Saiz et al. [101] evaluated the *in vitro* response in SBF of silicate glass coating on Ti–6Al–4V. Glasses belonging to the SiO_2 –CaO–MgO– Na_2O – K_2O – P_2O_5 system were used to prepare 50–70 μm thick coatings by employing a simple enameling technique. It has been found that (i) coatings with silica content lower than 60 wt% are more susceptible to corrosion and precipitate carbonated HA on their surface during *in vitro* tests; however (ii) these coatings have a higher thermal expansion than the metal and are under tension, (iii) after 2 month in SBF, cracks grow in the coating, reach the glass–metal interface, and initiate delamination, and (iv) glasses with silica content higher than 60 wt% are more resistant to corrosion and have lower thermal expansion, and these coatings do not crack, but such glasses with silica do not precipitate AP even after 2 months in SBF [101]. Lee et al. [102] prepared calcium-phosphate, AP-wollastonite (CaSiO_3) (1:3 by volume fraction) glass ceramic, AP-wollastonite (1:1) glass ceramic, and bioactive CaO – SiO_2 – B_2O_3 glass ceramic coatings by the dipping method. Coated and uncoated Ti–6Al–4V screws were inserted into the tibia of 18 adult mongrel male dogs for 2, 4, and 8 weeks. It was found that (i) at 2, 4, and 8 weeks,

the extraction torque of these ceramic-coated screws was significantly higher than the corresponding insertion torque and (ii) strong fixation was observed even at 2 weeks in all the three coatings except $\text{CaO-SiO}_2\text{-B}_2\text{O}_3$ glass ceramic coating [102].

The efficacy of a BAG-ceramic (Biosilicate[®]) and a BAG (Biogran[®]) placed in dental sockets in the maintenance of alveolar ridge and in the osteointegration of Ti implants was examined. Six dogs had their low premolars extracted and the sockets were implanted with Biosilicate[®], Biogran[®] particles, or left untreated. After the extractions, measurements of width and height on the alveolar ridge were taken. After 12 weeks a new surgery was performed to take the final ridge measurements and to insert bilaterally three Ti implants in biomaterial-implanted and control sites. Eight weeks postimplantation, block biopsies were processed for histological and histomorphometric analysis. The percentages of BIC of mineralized BABT and of mineralized BAMA were determined. It was found that (i) the presence of Biosilicate[®] or Biogran[®] particles preserved alveolar ridge height without affecting its width, and (ii) no significant differences in terms of BIC, BAMA, and BABT values were detected among Biosilicate[®], Biogran[®], and the nonimplanted group, concluding that filling of sockets with either Biosilicate[®] or Biogran[®] particles preserves alveolar bone ridge height and allows osseointegration of Ti implants [103]. The use of different bioactive materials as a coating on dental implant to restore tooth function is a growing trend in modern dentistry. HA and the BAG-coated implants were evaluated for their behavior in osseous tissue following implantation in 14 patients. BAG and HA formulated and prepared for coating on Ti-6Al-4V alloy. HA coating was applied on the implant surface by an air plasma spray technique and BAG coating was applied by a vitreous enameling technique. Their outcome was assessed after a 6-month *in vivo* study in humans. It was reported that (i) HA and BAG coating materials were nontoxic and biocompatible and (ii) uneventful healing was observed with both types of implants. It was concluded that BAG is a good alternative coating material for dental implants [104].

The host response to titanium alloy (Ti-6Al-4V) is not always favorable as a fibrous layer may form at the skeletal tissue-device interface, causing aseptic loosening. Recently, sphene (CaTiSiO_5) ceramics were developed by incorporating Ti in the Ca-Si system and found to exhibit improved chemical stability. The *in vitro* response of human osteoblast-like cells, human osteoclasts, and human microvascular endothelial cells was evaluated to sphene ceramics and it was determined whether coating Ti-6Al-4V implants with sphene enhances anchorage to surrounding bone. It was shown that (i) sphene ceramics support human osteoblast-like cell attachment with organized cytoskeleton structure and express increased mRNA levels of osteoblast-related genes, (ii) sphene ceramics were able to induce the differentiation of monocytes to form functional osteoclasts with the characteristic features of f-actin and $\alpha_v\beta_3$ integrin, and express osteoclast-related genes, and (iii) human endothelial cells were also able to attach and express the endothelial cell markers ZO-1 and VE-Cadherin when

cultured on sphene ceramics. Histological staining, enzyme histochemistry, and immunolabeling were used for identification of mineralized bone and bone remodeling around the coated implants. Ti–6Al–4V implants coated with sphene showed new bone formation and filled the gap between the implants and existing bone in a manner comparable to that of the HA coatings used as control. The new bone was in direct contact with the implants, whereas fibrous tissue formed between the bone and implant with uncoated Ti–6Al–4V. It was further mentioned that the *in vivo* assessment of sphene-coated implants supports this *in vitro* observation, suggesting that they have the ability to recruit osteogenic cells, and thus support bone formation around the implants and enhance osteointegration [105].

Calcium phosphate ceramics are widely used as coating materials for orthopedic implants and are found to enhance initial bony ingrowth by stimulating osseous apposition to the implant surface. Two novel calcium orthophosphate materials were selected for coating onto the commonly used orthopedic implant material Ti–6Al–4V. One was calcium alkali orthophosphate with the crystal-line phase $\text{Ca}_{10}[\text{K/Na}](\text{PO}_4)_7$ with a small addition of SiO_2 and the other was calcium orthophosphate composed of 70 mol% fluorapatite, $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$, and 30 mol% $\text{CaZr}_4(\text{PO}_4)_6$. The coated implants were placed in cortical and corticocancellous bone of sheep femurs for 6 weeks. Retrieved samples were tested for osseointegration and mechanical strength. It was found that both coatings produced an enhanced bone–implant contact rate compared to the control when implanted in corticocancellous bone, indicating that the two coatings have the capability of encouraging bone growth, and hence the potential for being used as coating materials on Ti implants [106].

A surface-reforming technique for improving the biocompatibility of titanium materials and increasing the possibilities for producing artificial bones and artificial tooth roots was developed. A porous ceramic film (or oxide film) was formed by anodizing in an electrolyte containing BMP. The spark discharge will be instantaneous but shifts from one to another, so numerous minute pores with a diameter of about $3\text{ }\mu\text{m}$ will form in the film to permit BMP fixation on the porous substance. BMP is a bone derivative substance contained in animal bones, teeth, and tusks. It generates new bones even inside muscles, so it is highly promising for applications involving the production of artificial bones. It was reported that the yield of BMP is extremely low with 0.001% of bone, but by reforming the titanium surface, bones can be introduced efficiently with an extremely small amount of BMP [107].

11.4.2 HA Coating

There are a quite large number of published articles on HA from various viewpoints, including a variety of processes and methods to produce HA, characterizations, property evaluations, and clinical evaluations.

Manufacturing Process and Methods

Enhancement of the osteoconductivity² of Ti implants is potentially beneficial to patients since it shortens the medical treatment time and increases the initial stability of the implant. To achieve better osteoconductivity, an AP $[\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}]$ coating has been commonly employed on the Ti implant surface.

Bigi et al. [108] performed a fast biomimetic deposition of HA coatings on Ti–6Al–4V substrates using a slightly supersaturated Ca/P solution, with an ionic composition simpler than that of SBF to fabricate nanocrystalline HA. It was found that (i) soaking in supersaturated Ca/P solution results in the deposition of a uniform coating in a few hours, whereas SBF, or even $1.5 \times \text{SBF}$, requires 14 days to deposit a homogeneous coating on the same substrates, (ii) the coating consists of HA globular aggregates, that exhibit a finer lamellar structure than those deposited from SBF, and (iii) the extent of deposition increases on increasing the immersion time [108].

HA is a major mineral component in animal and human bodies. It has been used widely not only as a biomedical implant material but also as biological chromatography that supports in protein purification and DNA isolation. Spherical HA ceramic beads have recently been developed that show improvements in mechanical properties and physical and chemical stability. These spherical ceramic beads are typically 20–80 μm in size. There are advantages to reducing the granule size of the spherical HA material: (1) the smaller the granule size, the higher the specific surface area and the higher the bonding capacity, (2) theoretically, the specific surface area (i.e., surface area per volume) is proportional to $6/d$, where d is the diameter of the spherical granule, (3) in addition, the mechanical properties of a packed column can be improved by reducing the granule size, resulting in more contacting surface areas, and thereby greater frictional forces between granules, and (4) furthermore, a uniform pack is expected to have a homogeneous pore

² Osteogenesis—development of bones (bone formation).

Osteoconduction—process in which a graft acts as a frame network or scaffold over which new host bone can grow.

Osteoinduction—processes in which new bone is induced to form through the activation of factors contained within the graft bone, such as proteins of growth factors. Furthermore, there are four different types of biomaterials exhibiting osteogenesis:

1. Distance osteogenesis: These types of materials are not in contact with living tissue, but they are not rejected by living tissue either. They are covered with connective tissue and do not connect to bone. Such materials (like Ti and Au) are called biotolerant.
2. Contact osteogenesis: Although it is possible for biomaterials to connect the bone through the connective tissue, they do not connect bone directly. Such materials (like Al_2O_3 or ZrO_2) are called bioinert.
3. Bonding osteogenesis: Bone can grow on biomaterials and can connect to bone directly. Such materials (like high dense sintered HA or bioactive glass) are called bioactive.
4. Osteogenesis: Materials are absorbed by osteoclasts, and bone can grow through the bone remodeling. Such materials (like low crystalline-type HA and TCP) are called bioresorbable.

distribution. The porosity and the specific surface areas of the HA material can be controlled by changing the morphology of the granules; for example, the solid spheres and doughnuts. Hence, Luo et al. [109] introduced a new method to produce spherical HA granules ranging in size from 1 to 8 μm with controlled morphology. This method involves an initial precipitation followed by a spray-drying process, which is the controlling step, to produce granules with various structures. It was reported that by adjusting the operating parameters (e.g., atomization pressure) and starting slurry (e.g., concentration), the hollow or solid spheres and doughnut-shaped HA were fabricated.

The porous HA coating on Ti implant materials was prepared by the process of electrodeposition, hydrothermal, and sinter. The surface morphology, bond strength, and thickness of HA coatings were investigated by SEM and AFM, and its biocompatibility was evaluated by cytotoxicity experiments and implant experiments, respectively. Results showed that (i) the HA coatings was 50- μm thickness and adhered on the Ti substrate strongly and bond strength reached 38 MPa, (ii) AFM analysis showed that the HA coating was a porous structure, in which the mean pore size was 236.5 μm , and (iii) cytotoxicity experiments and implant experiments showed that HA-coated Ti implant materials have little cytotoxicity *in vitro* and little inflammatory reaction *in vivo*, and there were no statistical disparities between HA-coated Ti implant and titanium implant materials of clinical application, demonstrating that HA-coated Ti has a good biocompatibility [110].

A thermally induced liquid-phase deposition method was employed to produce a thin HA film on a titanium substrate in a metastable calcium phosphate solution. Titanium foil of $100 \times 10 \times 0.02 \text{ mm}^3$ was used as a substrate. Prior to HA coating, the substrate was immersed in 5 M NaOH solution at 60°C for 24 h. Substrate temperature was kept constant at 60°C for 0.5–3 h by electrical heating with a DC power source in the metastable calcium phosphate solution. An X-ray diffractogram indicated that the film deposited on the titanium substrate was composed of HA. The amount of HA deposited increased with increase in heating time. These results suggested that a uniform HA film can be formed by simple chemical and thermal treatments. Based on the results, it was concluded that this technique seemed to be useful for producing uniform HA coatings on complex-shaped and porous dental implants [111].

With the growing demands of bioactive materials for orthopedic as well as maxillofacial surgery, the utilization of HA (HA: $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$, with Ca/P = 1.67) and TCP (TCP: $[\text{Ca}_3(\text{PO}_4)_6]$, with Ca/P = 1.50) as fillers, spacers, and bone graft substitutes has received great attention during the past two to three decades, primarily because of their biocompatibility, bioactivity, and osteoconduction characteristics with respect to host tissue. Porous HA granules with controlled porosity, pore size, pore size distribution, and granule size were fabricated using a drip-casting process. Granules with a wide range of porosity from 24 to 76 vol.%, pore size from 95 to 400 μm , and granular sizes from 0.7 to 4 mm can be obtained. This technique allows the fabrication of porous granules with desirable porous characters simulating natural bone architecture and is expected to provide advantages for biomedical purposes [112].

A novel method to rapidly deposit bone AP-like coatings on titanium implants in SBF is proposed by Han et al. [113]. The processing composed of two steps: MAO of titanium to form titania (TiO_2) films and UV-light illumination of the titania-coated titanium in SBF. It was reported that (i) the MAO films were porous and nanocrystalline, with pore sizes varying from 1 to 3 μm and grain sizes varying from 10–20 to 70–80 nm; the predominant phase in titania films changed from anatase to rutile, and the bond strength of the films decreased from 43.4 to 32.9 MPa as the applied voltage increased from 250 to 400 V, (ii) after UV-light illumination of the films in SBF for 2 h, bone AP-like coating was deposited on the MAO film formed at 250 V, and (iii) the bond strength of the AP/titania bilayer was about 44.2 MPa [113].

The sol method introduced by Kim et al. [114] was further developed using the sol–gel method to coat the Ti surface with HA films [115]. The coating properties, such as crystallinity and surface roughness, were controlled and their effects on the osteoblast-like cell responses were investigated. The obtained sol–gel films had a dense and homogeneous structure with a thickness of about 1 μm . It was found that (i) the heat-treated film at higher temperature had enhanced crystallinity ($600^\circ\text{C} > 500^\circ\text{C} > 400^\circ\text{C}$), while retaining similar surface roughness, (ii) when heat treated rapidly ($50^\circ\text{C}/\text{min}$), the film became quite rough, with roughness parameters being much higher (4–6 times) than that obtained at a low heating rate ($1^\circ\text{C}/\text{min}$), and (iii) the dissolution rate of the film decreased with increasing crystallinity ($400^\circ\text{C} > 500^\circ\text{C} > 600^\circ\text{C}$), and the rougher film had a slightly higher dissolution rate. The attachment, proliferation, and differentiation behaviors of human osteosarcoma (HOS) TE85 cells were affected by the properties of these films. It was further reported that (i) on the films with higher crystallinity (heat treated over 500°C), the cells attached and proliferated well, and expressed ALP and OC to a higher degree as compared to the poorly crystallized film (heat treated at 400°C) and (ii) on the rough film, the cell attachment was enhanced, but the ALP and OC expression levels were similar as compared to the smooth films [115].

The sol–gel method was favored due to the chemical homogeneity and fine grain size of the resultant coating, and the low crystallization temperature and mass producibility of the process itself. The sol–gel-derived HA and TiO_2 films, with thicknesses of about 800 and 200 nm, adhered tightly to each other and to the CpTi (grade II) substrate. It was reported that (i) the highest bond strength of the double layer coating was 55 MPa after heat treatment at 500°C due to enhanced chemical affinity of TiO_2 toward the HA layer, as well as toward the Ti substrate, (ii) human osteoblast-like cells, cultured on the HA/ TiO_2 coating surface, proliferated in a similar manner to those on the TiO_2 single coating and on the CpTi surfaces; however (iii) ALP activity of the cells on the HA/ TiO_2 double was expressed to a higher degree than on the TiO_2 single coating and CpTi surfaces, and (iv) the corrosion resistance of Ti was improved by the presence of the TiO_2 coating, as confirmed by a potentiodynamic polarization test [116]. Sol–gel-derived TiO_2 coatings are known to promote bone-like HA formation on their surfaces *in vitro* and *in vivo*. HA integrates into bone tissue. In some clinical applications, the surface of an implant is simultaneously interfaced with soft and hard tissues, so it should match

the properties of both. Moritz et al. [117] introduced a new method for treating the coatings locally in a controlled manner. The local densification of sol–gel-derived titania coatings on titanium substrates with a CO₂ laser was studied in terms of the *in vitro* calcium phosphate–inducing properties. The CO₂-laser–treated multilayer coating was compared with furnace-fired coating. Additionally, local areas of furnace-fired multilayer coatings were further laser-treated to achieve various properties in the same implant. It was found that (i) calcium phosphate formation can be adjusted locally by laser treatment, (ii) calcium phosphate is a bone-like HA, and (iii) the local treatment of sol–gel-derived coatings with a CO₂ laser is a promising technique for creating implants with various properties to interface different tissues, and a possible way of coating implants that do not tolerate furnace firing [117].

More economical and rapid bioceramic coating on the most common implant substrates such as Ti–6Al–4V and 316L SS used often in orthopedics has been developed [118]. For ceramic dip coating of implant substrates, HA powder, Ca₁₀(PO₄)₆(OH)₂, P₂O₅, Na₂CO₃, and KH₂PO₄ are used to provide the gel. Ceramic films on sandblasted substrates have been deposited by using a newly manufactured dip-coating apparatus. Sample characterization is evaluated by SEM and XRD analysis. Smooth and homogeneous coating films have been obtained and average of 20 MPa bonding strength has been achieved for both Ti–6Al–4V and 316L SS alloys after sintering at 750°C under flowing argon. It was mentioned that the current process appears to be cheap, easy, and flexible to shape variations and high production rates for orthopedic applications [118].

PSHA coatings on commercial orthopedic and dental implants consist of mixtures of calcium phosphate phases, predominantly a crystalline calcium phosphate phase, HA, and an amorphous calcium phosphate with varying ratios. Alternatives to the plasma-spray method are being explored because of some of its disadvantages, as mentioned earlier. Rohanizaded et al. [119] developed a two-step (immersion and hydrolysis) method to deposit an adherent AP coating on titanium substrate. First, titanium substrates were immersed in an acidic solution of calcium phosphate, resulting in the deposition of a monetite (CaHPO₄) coating. Second, the monetite crystals were transformed to AP by hydrolysis in a NaOH solution. EDS had revealed the presence of calcium and phosphorous elements on the titanium substrate after removing the coating using tensile or scratching tests. It was reported that (i) the average tensile bond of the coating was 5.2 MPa, and cohesion failures were observed more frequently than adhesion failures, (ii) this method has the advantage of producing a coating with homogenous composition on even implants of complex geometry or porosity, and (iii) this method involves low temperatures and, therefore, can allow the incorporation of growth factors or biogenic molecules [119].

Depending on the coating method utilized and subsequent heat treatments (such as through the use of plasma-spray deposition), interdiffusion of atomic species across Ti and HA coatings may result. These events may lead to structural and compositional changes that consequently cause unexpected HA phase transformations which may clearly influence the performance of an orthopedic implant. The

in vitro study was conducted to compare the cytocompatibility properties of chemistries that may form at the Ti–HA interface, specifically HA, TCP, HA doped with Ti, and those containing calcium titanate (CaTiO_3). It was reported that (i) osteoblast (bone-forming cells) adhesion increased with greater CaTiO_3 substitutions in either HA or TCP, (ii) specifically, osteoblast adhesion on HA and TCP composites with CaTiO_3 was almost 4.5 times higher than that over pure HA, (iii) material characterization studies revealed that enhanced osteoblast adhesion on these compacts may be due to increasing shrinkage in the unit lattice parameters and decreasing grain size, and (iv) although all CaTiO_3 composites exhibited excellent osteoblast adhesion results, $\text{Ca}_9\text{HPO}_4(\text{PO}_4)_5\text{OH}$ phase transformation into TCP/ CaTiO_3 increased osteoblast adhesion the most. For these reasons, it was mentioned that these materials should be further studied for orthopedic applications [120].

As has been reviewed earlier, a plasma spray method has been widely accepted as the AP coating method because it gives tight adhesion between the AP coating and Ti. However, the plasma spray method employs extremely high temperatures ($10,000^\circ\text{C}$ – $12,000^\circ\text{C}$) during the coating process. Unfortunately, it results in potentially serious problems including (1) an alteration of structure, (2) formation of AP with extremely high crystallinity, and (3) long-term dissolution and the accompanying debonding of the coating layer. To reduce these drawbacks associated with the conventional plasma spray method, a high-viscosity flame spray method was developed. Although the high-viscosity flame spray method employs a lower temperature compared with the plasma spray method, it is still 3000°C , which is adequate to alter the crystal structure and formation of AP with extremely high crystallinity. To avoid these drawbacks associated with AP coating methods using high temperatures, many alternative room-temperature coating methods were studied extensively including ion beam sputtering, dipping, electrophoretic deposition, and electrochemical deposition [121]. Mano et al. [121] developed a new coating method called blast coating, using common sandblasting equipment at room temperature. Blast-AP coated CpTi implants were inserted in the tibiae of rats for 1, 3, and 6 weeks. It was found that (i) the AP coating adhered tightly to the Ti surface even after the 6-week implantation, (ii) the implants cause no inflammatory response, showing strong bone response and much better osteoconductivity compared with the uncoated CpTi implant, and (iii) the new bone formed on the surface of coated implants was thinner compared with that formed on the surface of the Ti implant. Therefore, the blast–AP implant has a good potential as an osteoconductive implant material [121].

Wang et al. [122] investigated the bond strength of an AP layer on Ti substrate coated by biomimetic method and to improve the bonding of an AP layer to Ti substrate by optimizing the alkali heat-treatment process. Ti plates pretreated with an alkali solution of 10 mol NaOH were heat treated at 600°C for 1 h at different atmospheres (in air and in vacuum). A dense AP layer formed on top of the sodium titanate layer after soaking the alkali and heat-treated Ti samples in SBF for up to 3 weeks. The bond strengths of the sodium titanate layer on Ti substrate, and the AP layer on the sodium titanate layer, were measured, respectively, by applying a

tensile load. The fracture sites were observed with a SEM. It was reported that (i) the AP layer on the substrate after alkali heat treatment in air achieved higher bond strength than that on the substrate after alkali heat treatment in vacuum and (ii) the interfacial structure between the sodium titanate and Ti substrate has a significant influence on the bond strength of the AP layer. Hence, it was concluded that titanium implants can achieve better osteointegration under load-bearing conditions by depositing an AP layer *in vivo* on a Ti surface subjected to alkali and heat treated in air [122].

PSHA-coated implants show failures along the coating–substrate interface due to poor bond strength. HA coatings obtained by pulsed laser deposition (PLD) were analyzed and compared to commercially used plasma-sprayed coatings with respect to their bond strength to Ti–6Al–4V, as well as surface roughness alterations produced by each of the two deposition methods. Twelve Ti–6Al–4V disks were plasma sprayed under commercial implant coating conditions, and 24 Ti–6Al–4V disks were coated using PLD. All coatings were characterized by the presence of the different calcium phosphate (Ca-P) phases. The plasma-sprayed coatings were predominantly HA, and the pulsed laser-deposited coatings were HA and HA coating with a tetra calcium phosphate phase. The surface roughness was analyzed before and after the coating processes to assess roughness changes to the surface due to the coatings. The adhesive bond strengths of these coatings to the substrate alloy were tested and compared. It was found that the surface roughness alteration following PLD was a decrease of 0.2 mm, whereas following plasma-spraying the decrease was 1.0 μm , (ii) bond strengths of 68.3 MPa for pulsed laser-deposited HA coatings, 55.2 MPa for pulsed laser-deposited HA with tetra-Ca-P, and 17 MPa for PSHA, concluding that HA coatings obtained by PLD showed greater adherence to titanium alloy and PLD offers an alternative method to produce thinner coatings with better adherence properties, along with precise control over the deposition process [123].

There have been several studies done on AP-like formation without HA coating. Ti can form a bone-like AP layer on its surface in SBF when it is treated in NaOH. When pretreated Ti is exposed to SBF, the alkali ions are released from the surface into the surrounding fluid. The sodium ions increase the degree of supersaturation of the soaking solution with respect to AP by increasing pH. On the other hand, the released Na^+ causes an increase in external alkalinity that triggers an inflammatory response and leads to cell death. Therefore, it would be beneficial to decrease the release of Na^+ into the surrounding tissue. It was found that (i) the rate of AP formation was not significantly influenced by a lower amount of Na^+ ion in the surface layer and (ii) Ti with the lowest content of Na^+ could be more suitable for implantation in the human body (4 at.%) [124]. Jonášová et al. [125] pretreated CpTi surfaces: (1) in 10 M NaOH at 60°C for 24 h and (2) etched in HCl under inert atmosphere of CO_2 for 2 h, followed by 10 M NaOH treatment. It was found that Ti treated in NaOH can form hydroxycarbonated AP after exposition in SBF. Generally, Ti is covered with a passive oxide layer. In NaOH this passive film dissolves and an amorphous layer containing alkali ions is formed. When exposed to SBF, the alkali ions are released from the amorphous layer and hydronium ions

enter into the surface layer, resulting in the formation of Ti–OH groups in the surface. The acid-etching of Ti in HCl under inert atmosphere leads to the formation of a microroughened surface, which remains after alkali treatment in NaOH. It was shown that the AP nucleation was uniform and the thickness of the precipitated hydroxycarbonated AP layer increased continuously with time. The treatment of Ti by acid-etching in HCl, and subsequently in NaOH, is a suitable method for providing the metal implant with bone-bonding ability [125]. Wang et al. [126] reported that bone-like AP was formed on Ti–6Al–4V surfaces pretreated in NaOH solution immersed in SBF, while no AP was formed on untreated Ti–6Al–4V. The increase in electrical resistance (by EIS) in the outermost surface of pretreated Ti–6Al–4V indicated AP nucleation. With an increase in immersion time in SBF, islands of AP were seen to grow and coalesce on pretreated Ti–6Al–4V under SEM. It was also mentioned that the growth of AP corresponded to the increase in electrical resistance of the surface layer [126].

Titania-based films on Ti were prepared by MAO at various applied voltages (250–500 V) in electrolytic solution containing β -glycerophosphate disodium salt pentahydrate (β -GP) and calcium acetate monohydrate. Such modified Ti samples were examined in SBF and 1.5 times concentrated SBF [127]. It was found that (i) macroporous, Ca- and P-containing titania-based films were formed on the Ti substrates, (ii) in particular, Ca- and P-containing compounds such as CaTiO_3 , $\beta\text{-Ca}_2\text{P}_2\text{O}_7$, and $\alpha\text{-Ca}_3(\text{PO}_4)_2$ were produced at higher voltage (> 450 V), (iii) when immersed in SBF, a carbonated HA was induced on the surface at 450 V after 28 days, which is closely related to Ca- and P-containing phases, and (iv) the use of 1.5 concentrated SBF shortened the AP induction time, and AP formation was confirmed even on the surface of the films oxidized at 350 V, suggesting that the incorporated Ca and P in the titania films play a similar role to the Ca- and P-containing compounds in the SBF [127–129].

HA can be admixed with Ti powder. 80HA–20Ti powder and 90HA–10Ti powder (by wt%) were mechanically mixed and dry-pressed, and heat treated at 1100°C for 30 min in vacuum ($< 6 \times 10^{-3}$ Pa). Heat treatment of HA specimens in vacuum resulted in the loss of hydroxyl groups, as well as the formation of a secondary β -TCP phase. It was concluded that the *in vacuo* heat treatment process completely converted the metal-ceramic composites to ceramic composites [130]. Moreover, using air plasma-spraying and vacuum plasma-spraying methods, HA and a mixture of HA + Ti were deposited on Ti–6Al–4V. It was reported that a higher adhesion was obtained with vacuum plasma-spraying rather than with air plasma-spraying [131].

Lee et al. [132] employed the electron-beam deposition method to obtain a series of fluoridated AP coatings. The fluoridation of AP was aimed to improve the stability of the coating and elicit the fluoride effect, which is useful in dental restoration. AP fluoridated at different levels was used as initial evaporants for the coatings. It was observed that (i) the as-deposited coatings were amorphous, but after heat-treated at 500°C for 1 h, the coatings crystallized well to an AP phase without forming any cracks, (ii) the adhesion strengths of the as-deposited coatings were about 40 MPa, and after heat treatment at 500°C, it decreased to about 20 MPa;

however, the partially fluoridated coating maintained its initial strength. It was also reported that (i) the osteoblast-like cells responded to the coatings in a similar manner to the dissolution behavior, (ii) the cells on the fluoridate coatings showed a lower proliferation level compared to those on the pure HA coating, and (iii) the ALP activity of the cells was slightly lower than of on the pure HA coating [132]. Kim et al. [114] deposited HA and fluoridated HA films on CpTi (grade II). HA sol was prepared by mixing $P(C_2H_5O)_3$ and distilled water, and fluoridated HA sol was prepared by NH_4F in a P-containing solution (like HA by replacing the OH group with F ions), and their films were deposited on CpTi (grade II). The mixture was stirred at room temperature for 72 h. Dipping CpTi into the solutions was performed at $500^\circ C$ for 1 h. It was reported that (i) the coatings layers were dense, uniform, and had a thickness of approximately $5\text{ }\mu m$ after heat treatment at $500^\circ C$, (ii) the fluoridated HA layer showed much lower dissolution rate (in 0.9% NaCl as physiological saline solution) than pure HA, suggesting the tailoring of solubility with F-incorporation within the AP structure, (iii) the osteoblast-like MG63 and HOS cells grew and proliferated favorably on both coatings and pure Ti, and (iv) especially, both coated Ti exhibited higher ALP expression levels as compared to noncoated Ti, confirming the improved activity and functionality of cells on the substrate via the coatings [114].

A novel hybrid coating process, combining NanoSpray[®] (built on electrostatic spray coating) technology with microwave sintering process, was developed for synthesizing a HA-based nanostructured coating with favorable properties for dental and orthopedic implants. Specifically, HA nanoparticles were deposited on CpTi substrates using NanoSpray technique to produce the HA coating, which was then sintered in a microwave furnace under controlled conditions. The study showed that the use of NanoSpray followed by microwave sintering results in a nanoscale HA coating for dental/orthopedic applications [133].

Skeletal bone consists of HA and collagen type I, both of which are osseointegrative. The goal of osseointegration of orthopedic and dental implants is the rapid achievement of a mechanically stable long-lasting fixation between bone and an implant surface. Daugaard et al. [134] evaluated the mechanical fixation and tissue distribution surrounding implants coated with three surfaces: a PSHA coating, a thinner coating of electrochemical-assisted deposition of HA, and an identical thin coating with a top layer of mineralized collagen. Uncoated plasma-sprayed Ti–6Al–4V alloy served as a negative control. The electrochemical-assisted deposition was performed near physiological conditions. A canine experimental joint replacement model was used with four cylindrical implants (one of each treatment group) inserted in the humeri cancellous metaphyseal bone in a 1 mm gap. Observation time was 4 weeks. The mechanical fixation was quantified by push-out test to failure and the peri-implant tissue formation by histomorphometric evaluation. It was found that (i) HA coatings deposited either by plasma spray technique or electrochemically increased the mechanical fixation and bone ingrowth, but there was no statistical difference between the individual HA applications and (ii) addition of collagen to the mineralized phase of the coating to create a more bone natural surface did not improve the osseointegrative effect of HA [134].

Dental implant failure often occurs due to oral bacterial infection. It was demonstrated that antibiotic efficacy could be enhanced with modified titanium. First, the titanium was modified by anodization and heat-treatment. Then, a biomimetic coating process was completed in two steps. Surface characterization was performed with SEM, EDS, and XRD. Release of antibiotic was evaluated by UV/VIS spectrometry, and the antibacterial effect was evaluated on *Streptococcus mutans*. After the second coating step, it was observed that a thick homogeneous AP layer contained the antibiotic cefalotin. The titanium formed a rutile phase after the heat treatment, and a carbonated AP phase appeared after biomimetic coating. It was reported that (i) the modified titanium increased the loading of cefalotin onto the HA-coated surface and (ii) modified titanium coated with a cefalotin using biomimetic coating method might be useful for preventing local postsurgical implant infections [135].

Ahmed et al. [136] evaluated the bone tissue response to strontium- and silicon-substituted AP (Sr-HA and Si-HA) modified Ti implants. Sr-HA, Si-HA, and HA were grown on thermally oxidized Ti implants by a biomimetic process. Oxidized implants were used as controls. Surface properties, that is, chemical composition, surface thickness, morphology/pore characteristics, crystal structure and roughness, were characterized with various analytical techniques. The implants were inserted in rat tibiae and block biopsies were prepared for histology, histomorphometry, and SEM analysis. It was observed that (i) histologically, new bone formed on all implant surfaces, (ii) the bone was deposited directly onto the Sr-HA and Si-HA implants without any intervening soft tissue, (iii) the statistical analysis showed a significantly higher amount of BIC ratio for the Si-doped HA modification and a significantly higher BA for the Sr-doped HA modification when compared with the nondoped HA modification; the differences were most pronounced at the early time point, and (iv) the healing time had a significant impact for both BA and BIC. It was concluded that biomimetically prepared Si-HA and Sr-HA on Ti implants provided bioactivity and promoted early bone formation [136].

Roy et al. [137] reported fabrication of strontium- (Sr) and magnesium (Mg)-doped HA coating on CpTi substrates using inductively coupled radio frequency (RF) plasma spray. HA powder was doped with 1 wt % Sr (Sr-HA) and 1 wt % Mg (Mg-HA), heat-treated at 800°C for 6 h and then used for plasma spray coating. There are several interesting results as follows. XRD and FTIR analysis indicated that the coatings were primarily composed of phase pure crystalline HA. When compared to undoped HA coating, physical properties such as microstructure, grain size, and adhesive bond strength of the doped HA coatings did not change significantly. Microstructure of the coatings showed coherency in the structure with an average grain size of 200–280 μm HA particles, where each of the HA grains consisted of 20–30 nm sized particles. An average adhesive bond strength of 17 MPa ensured sufficient mechanical strength of the coatings. A chemistry-dependent improvement in bone cell–coating interaction was noticed for doped coatings although it had minimal effect on physical properties of the coatings. *In vitro* cell–materials interactions using human fetal osteoblasts (hFOB) showed better cell attachment and proliferation on Sr-HA coatings compared to HA or Mg-HA

coatings. Presence of Sr in the coating also stimulated hFOB cell differentiation and ALP expression. Based on these findings, it was concluded that improvement in bioactivity of Sr-doped HA coatings on Ti without compromising its mechanical properties makes it an excellent material of choice for coated implants [137].

Osteointegration, in terms of the bone apposition ratio (BAR) and the new bone area (NBA), was measured by backscattered electron imaging. The results were compared for four implant types: grit-blasted and NaOH-treated Ti–6Al–4V (uncoated NaOH), electrodeposited with HA without alkali treatment (ED-HAp), electrodeposited with HA after alkali treatment (NaOH-ED-HAp), and plasma sprayed with HA (PSHA). No heat treatment was done after soaking in NaOH. The implants were press-fitted into the intramedullary canal of mature New Zealand white rabbits and analyzed both at the diaphyseal and at the metaphyseal zones, either 1 week or 12 weeks after surgery. It was reported that (i) NaOH-ED-HAp already exhibited a higher BAR value than the ED-HAp at 1 week, and was as good as the commercial PSHA at 12 weeks, (ii) the NBA value for NaOH-ED-HAp at 12 weeks was the highest, and (iii) the higher content of octacalcium phosphate (OCP) in NaOH-ED-HAp, as evident from the XPS analysis of the oxygen shake-up peaks, and the associated increase in the solubility of this coating *in vivo* are considered responsible for the enhanced osseointegration. It was concluded that electrodeposition of HAp following soaking in NaOH may become an attractive alternative for the traditional plasma-sprayed process for coating of orthopedic and dental implants [138].

Property and Characterization

Souto et al. [139] investigated the corrosion behavior of four different preparations of PSHA coatings (50 and 200 μm) on Ti–6Al–4V substrates in static HBSS through DC potentiodynamic and AC EIS techniques. Because the coatings are porous, ionic paths between the electrolytic medium and the base material can eventually be produced, resulting in the corrosion of the coated metal. It was concluded that significant differences were found in electrochemical behavior for similar nominal thicknesses of HA coatings obtained under different spraying [139]. Filiaggi et al. [140] reported that evaluations of a HA-coated Ti–6Al–4V implant system using a modified short bar technique for interfacial fracture toughness determination revealed relatively low fracture toughness values. Using high-resolution electron spectroscopic imaging, evidence of chemical bonding was revealed at the PSHA/Ti–6Al–4V interface, although bonding was primarily due to mechanical interlocking at the interface [140]. The MOE, residual stress and strain, bonding strength, and microstructure of the PSHA coating were evaluated on Ti–6Al–4V substrate with and without immersion in HBSS. It was reported that (i) the residual stress and strain, MOE, and bonding strength of the PSHA coating after immersion in Hank's solution were substantially decreased and (ii) the decayed MOE and mechanical properties of HA coatings were caused by the degraded interlamellar or cohesive bonding in the coating due to the increased porosity after immersion that weakens the bonding strength of the coating and substrate system. It was also

suggested that the controlled residual stress and strain in the coating might promote the long-term stability of the PSHA-coated implant [141]. Yang et al. [142] investigated the effect of TPS and zirconia (ZrO_2)-coated titanium substrates on the adhesive, compositional, and structural properties of PSHA coatings. AP-type and α -TCP phases were observed for all the HA coatings. The coating surfaces appeared rough and melted, with surface roughness correlating to the size of the starting powder. It was found that (i) no significant difference in the Ca/P ratio of HA on Ti and TPS-coated Ti substrates was observed, (ii) however, the Ca/P ratio of HA on ZrO_2 -coated Ti substrate was significantly increased, (iii) interfaces between all coatings and substrates were observed to be dense and tightly bound, except for HA coatings on TPS-coated Ti substrate interface; however (iv) an intermediate TPS or ZrO_2 layer between the HA and Ti substrate resulted in a lower adhesive strength as compared to HA on Ti substrate [142].

There are several studies done on effects of postspray coating heat-treatment on mechanical and structural integrities of the coated film. A postplasma-spray heat treatment (at 960°C for 24 h followed by slow furnace cooling) was performed to enhance chemical bonding at the metal–ceramic interface, and hence improve the mechanical properties. It was found that any improvements realized were lost due to the chemical instability of the coating in a moisture-laden environment, with a concomitant loss in bonding properties, and this deterioration appeared to be related to environmentally assisted crack growth as influenced by processing conditions [143]. HA coatings on Ti–6Al–4V were annealed at 400°C in air for 90 h, and were evaluated as a postcoating heat treatment. It was found that (i) the oxide species TiO_2 , Al_2O_3 , V_2O_5 , V_2O_3 , and VO_2 were present on both as-coated and as heat-treated samples and (ii) the fatigue resistance of the substrate was found to be significantly reduced by the heat treatment, due to the stress relief [144]. Ti–6Al–4V substrate was heated at 25°C , 160°C , and 250°C , followed by cooling in air or air + CO_2 gas during operating of the HA plasma coating. It was reported that (i) when residual compressive stress was 17 MPa, the bonding strength was 9 MPa, while the bonding strength continuously reduced to 3 MPa for a residual compressive stress of about 23 MPa, and (ii) the compressive residual stress weakened the bonding at the interface of the HA and the Ti-substrate [145], due to remarkable mechanical mismatching.

Ergun et al. [146] studied the chemical reactions between HA and titanium in three different kinds of experiments to increase the understanding of the bond mechanisms of HA to titanium for implant materials. HA powder was bonded to a titanium rod with hot isostatic pressing. Interdiffusion of the HA elements and titanium was found in concentration profiles measured in the electron microprobe. Titanium was vapor-deposited on sintered HA disks and heated in air; perovskite (CaTiO_3) was found on the HA surface with Rutherford backscattering and XRD measurements. Powder composites of HA, titanium, and TiO_2 were sintered at 1100°C ; again, perovskite was a reaction product, as well as $\beta\text{-Ca}_3(\text{PO}_4)_2$, from a decomposition of the HA. Based on these findings, it was reported that (i) chemical reactions and interdiffusion between HA and TiO_2 during sintering resulted in chemical bonding between HA and titanium; thus, cracks and weakness at

HA–titanium interfaces probably result from mismatch between the coefficients of thermal expansion of these materials and (ii) HA composites with other ceramics and different alloys should lead to better thermal matching and better bonding at the interface [146].

There are several research works in regard to mechanical properties of HA and bond strength of HA layer. Cook et al. [147] conducted interface shear strength tests using a transcortical push-out model in dogs after 3, 5, 6, 10, and 32 weeks on CpTi-coated Ti–6Al–4V and HA-coated Ti–6Al–4V. The mean values for interface shear strength increased up to 7.27 MPa for HA-coated implants after 10 weeks of implantation, while uncoated CpTi had 1.54 MPa [147]. Yang et al. [148] reported that the direction of principal stresses were in proximity to and perpendicular to the spraying direction. The measured MOE of HA (16 GPa at maximum) was much lower than the theoretical value (i.e., 112 GPa). The denser, well-melted HA exhibited a higher residual stress (compressive, 10–15 MPa at maximum), as compared with the less dense, poor-melting HA. The denser coatings could be affected by higher plasma power and lower powder feed rate. It was also reported that the thicker 200 μm HA exhibited higher residual stress than that of the thinner 50 μm HA [148]. Mimura et al. [149] characterized morphologically and chemically the coating–substrate interface of a commercially available dental implant coated with PSHA, when subjected to mechanical environment. A thin Ti oxide film containing Ca and P was found at the interface on Ti–6Al–4V. When the implant was subjected to mechanical stress, a mixed mode of cohesive and interfacial fractures occurred. The cohesive fracture was due to separation of the oxide film from the substrate, while the interfacial fracture was due to the exfoliation of the coating from the oxide film bonded to the substrate. It was reported that (i) microanalytical results showed diffusion of Ca into the metal substrate, hence indicating the presence of chemical bond at the interface; however (ii) mechanical interlocking seemed to play the major role in the interfacial bond [149]. Lynn et al. [150] conducted uniaxial fatigue tests ($\sigma_{\text{max}}/\sigma_{\text{min}}$ stress ratio, $R = -1$, stress amplitude of 620 MPa, frequency of 50 Hz) on blasted-Ti–6Al–4V with HA coating on Ti–6Al–4V with film thickness ranging from 0, 25, 50, 75, 100, and 150 μm . It was found that (i) samples with 150 μm were shown to have significantly decreased fatigue resistance, while coatings of 25–100 μm were found to have no effect on fatigue resistance and (ii) HA coatings with 25–50 μm show no observable delamination during fatigue tests, while coatings with 75–150 μm thick were observed to spall following but not prior to the initiation of the first fatigue crack in the substrate [150].

Bioactive HA coating on titanium (Ti) implant can be used as a drug delivery device. A controlled release of drug around the implant requires the incorporation of drug into the coating material during the coating process. HA coating was prepared using a two-step procedure in conditions suitable for simultaneous incorporation of the protein-based drug into the coating material. Monetite (CaHPO_4) coating was deposited on Ti substrate in acidic condition followed by the transformation of the monetite coating to HA. It was reported that (i) XRD confirmed the formation of the monetite phase at the first step of the coating preparation, which was transformed

into HA at the second step and (ii) the critical shearing stress was found to be 84.20 MPa for the monetite coating and 44.40 MPa for the HA coating [151].

Thick bioceramic coatings like PSHA have been shown to increase the overall tissue response and biomechanical fixation of dental implants. However, the presence and potential fracture of a bone-coating—metallic substrate interface at long times after implantation led these implants to fall from favor in clinical practice. Coelho et al. [152] evaluated the biomechanical fixation and biological response of Ca- and P-based, 20–50 nm thickness bioceramic deposition on a previously alumina-blasted/acid-etched Ti–6Al–4V implant surface in a dog model. Cylindrical alumina-blasted/acid-etched (AB/AE) (control) and nanothickness bioceramic-coated AB/AE (nano) implant surfaces were surgically placed in dogs' proximal tibia and remained for 2 and 4 weeks *in vivo*. Following euthanization, the implants within surrounding bone tissue were mounted in epoxy and pulled out at a 0.5 mm/min rate. Following mechanical testing, the specimens were decalcified and processed for standard transmitted light microscopy evaluation. The BIC ratio to the pulled-out implant surface was determined. It was found that (i) no significant differences in pullout force were observed: 2 W Control (212.08 N), 2 W Nano (224.35 N), 4 W Control (207.07 N), and 4 W Nano (190.15 N), (ii) no significant differences were found in BIC ratio: 2 W Control (72.66%), 2 W Nano (69.44%), 4 W Control (70.44%), and 4 W Nano (69.11%), and (iii) 20–50 nm thickness bioceramic depositions onto previously alumina-blasted/acid-etched substrates did not improve the biomechanical fixation and the BIC at early implantation times [152].

Plasma-spray is a classical technique usually employed to cover orthopedic titanium implant surfaces with HA. Carradó et al. [153] investigated the structure and microstructure of HA plasma-spray 50 μm thick coating on Ti–6Al–4V and residual stress due to processing in the substrate and in HA coating. The structure of the coatings was determined by high-energy synchrotron XRD in energy dispersive (HESXRD), selected area electron diffraction (SAED), SEM, and FTIR. It was reported that (i) no impurity phases in the HA were identified by HESXRD to keep away from the decomposition of HA at high temperature, (ii) the morphology of HA powder observed by SEM exhibits grains of ca. 0.1 μm well adapted for cell proliferation, (iii) HA/Ti–6Al–4V interface observed by cross-section SEM and transmission electron microscopy (TEM) presents microcracks, and (iv) although the Ti substrates are in a slightly tensile residual state, the coated ones show a compressive state [153].

The success of implants in orthopedic and dental load-bearing applications crucially depends on the initial biological fixation of implants in surrounding bone tissues. Using HA coating on Ti implant as a carrier for BMPs may promote the osteointegration of implants and, therefore, reduce the risk of implant failure. HA coatings were deposited on six different groups of Ti surfaces: control (no pretreatment), pretreated with alkali, acid, heated at 800°C, grit-blasted with Al_2O_3 , and grit-blasted followed by heat treatment. HA coating was prepared using a two-step procedure. The first step was the chemical deposition of a monetite coating on Ti substrate in acidic condition at 75°C and the second step was the hydrolysis of the monetite coating to HA. The mechanical stability of the coatings deposited on the

pretreated substrates was assessed using a scratch test. It was reported that the coatings deposited on the grit-blasted Ti surface demonstrated superior adhesive properties with critical shearing stress 131.6 MPa [154].

PSHA-coated devices demonstrated wide variability in the percentage of the HA coating remaining on the stems. Porter et al. [155] reported that (i) the coating was missing from a substantial portion of a stem after only about 6 months of implantation and (ii) many ultrastructural features of the bone bonded to the HA coatings on these implants from human subjects were comparable to those on HA-coated devices implanted in a canine model. The geometric design and chemical compositions of an implant surface may play an important part in affecting early implant stabilization and influencing tissue healing.

The influence of different surface characteristics on bone integration of titanium implants was investigated by Buser et al. [156]. Hollow-cylinder implants with different surfaces were placed in the metaphyses of the tibia and femur in six miniature pigs. After 3 and 6 weeks, the implants with surrounding bone were removed and analyzed in undecalcified transverse sections. The histologic examination revealed direct bone–implant contact for all implants. However, the morphometric analyses demonstrated significant differences in the percentage of bone–implant contact, when measured in cancellous bone. It was reported that (i) electropolished, as well as the sandblasted and acid pickled (medium grit, HF/HNO₃) implant surfaces, had the lowest percentage of BIC ranging between 20% and 25%, (ii) sandblasted implants, with a large grit, and TPS implants demonstrated 30–40% in BIC, and (iii) the highest extent of BIC was observed in sandblasted and acid-attacked surfaces (large grit; HCl/H₂SO₄) with mean values of 50–60%, and HA-coated implants exhibited BIC of 60–70%. It was therefore concluded that the extent of the bone–implant interface is positively correlated with an increasing roughness of the implant surface. Moreover, the morphometric results indicated that (i) rough implant surfaces generally demonstrated an increase in bone apposition compared to polished or fine structured surfaces, (ii) the acid treatment with HCl/H₂SO₄ used for sandblasted with large grit implants has an additional stimulating influence on bone apposition, (iii) the HA-coated implants showed the highest extent of bone–implant interface, and (iv) the HA coating consistently revealed signs of resorption. It was suggested that sandblasting and chemical etching with HCl/H₂SO₄ as well as HA coating, seemed to be the most promising alternatives to titanium implants with smooth or TPS surfaces [156].

Clinical Evaluation and Beneficial Effects

Titanium and its alloys are the most widespread materials for the realization of orthopedic and dental implants due to their good mechanical properties and biocompatibility. Surface functionalization of biomaterials aimed to improve and quicken implant integration, and tissue regeneration is an active research field. The opportunity to confer biological activity (ability to directly stimulate cells with proper biological signals) to the Ti–6Al–4V alloy, previously modified to be bioactive from the inorganic point of view (AP precipitation) was explored. The ALP

enzyme was grafted to a metal surface via tresyl chloride activation, maintaining its activity. A synergistic effect between biological functionalization and inorganic bioactivity was observed [157]. Piattelli et al. [158] examined retrieved HA-coated CpTi implants from patients. It was reported that the bone–HA interface presented variable features: in some areas the mineralized bone was directly apposed to the HA surface, while in others unmineralized material, probably osteoid, was interposed [158]. The effects of HA coating and macrotexturing of Ti–6Al–4V were tested by Hayashi et al. [159]. Implants were inserted in dog's femoral condyles. It was demonstrated that when grooved Ti implants were used, the addition of HA coating significantly improved the biological fixation. In addition, a grooved depth of 1 mm was found to give significantly better fixation than 2 mm. When compared to implants with traditional diffusion-bonded bead-coated porous surfaces, HA-coated grooved Ti implants were found to show better fixation at 4 weeks after implantation, but significantly inferior fixation at 12 weeks. Hence, it was concluded that while a groove depth of 1 mm was optimal in HA-coated and further grooved Ti implants, they are still inferior to bead-coated Ti implants with respect to longer-term fixation [159]. This phenomenon is sometimes called rugophilia (the term “rugo” implies roughness). Two different groups of HA-coated and uncoated porous Ti implants, 250–350 μm - and 500–700 μm -diameter beads, were press-fitted into femoral canine cancellous bone for 12 weeks. It was reported that (i) the percentage of bone and bone index was higher in the HA-coated implants, when comparing HA-coated versus uncoated implants in the 250–350 μm bead diameter group, (ii) comparing 500–700 μm , bone ingrowth and bone depth penetration were higher in HA-coated samples, and (iii) the HA coating was an effective method for improving bone formation and ingrowth in the porous implants [160].

Several HA-coated and uncoated Ti–6Al–4V femoral endoprostheses were evaluated in adult dogs for 52 weeks. It was found that (i) histologic sections from the uncoated grooved implants showed no direct bone–implant apposition without any fibrous tissue interposition after up to 10 weeks and (ii) the HA-coated grooved implants demonstrated extensive direct bone-coating apposition after 5 weeks [161]. HA-coated cylindrical plugs of CpTi, CpTi screws, and partially HA-coated CpTi screws were inserted in the tibiae of adult New Zealand white rabbits for 3 months. The histological results demonstrated that although there were no marked differences in bony reaction at the cortical level to the different implant materials, HA coating appeared to induce more bone formation in the medullary cavity. It was also noted that 3 months after insertion, loss of coating thickness had occurred [162]. Threaded HA-coated CpTi implants were inserted in the rabbit tibial metaphysis. After 6 weeks and 1 year postinsertion, the semiloaded implants were histomorphometrically analyzed. It was reported that (i) there was more direct bony contact with the HA-coated implants after 6 weeks and (ii) 1 year after insertion, there was significantly more direct BIC with the uncoated CpTi controls, suggesting that the HA coating does not necessarily improve implant integration over a long time period [163]. After 6 or 12 weeks, four goats were used for mechanical tests and three for histology. To cope with the severe femoral bone stock loss encountered in revision surgery, impacted trabecular bone grafts were used in

combination with a HA-coated Ti stem. In this first experimental study, the results indicated that this technique had a high complication rate. However, it was shown that impacted grafts sustained the loaded stems and that incorporation of the graft occurred with a biomechanically stable implant. The technique allows gradual graft incorporation and stability, but more investigations are needed before its introduction into clinical practice [164]. Surface treatments, such as sandblasting or deposit or rough pure Ti obtained by vacuum plasma-spraying, bring about an increase of passive and corrosion current density values as a consequence of the increase of the surface exposed to the aggressive environment. It should, however, be outlined that in the case of rough Ti, only Ti ions are released instead of Al or V out of Ti-6Al-4V. The presence of deposits of HA by vacuum plasma-spraying causes an increase of about one order of magnitude in the passive and corrosion current density of the metallic substrate [165].

Hayashi et al. [166] evaluated the bone-implant interface shear strength of HA-coated Ti-6Al-4V and HA-coated Ti-6Al-4V with a rougher surface in a trans-cortical model in adult dogs for 4 and 12 weeks. It was reported that (i) the bone-implant shear strength of bead-coated porous Ti-6Al-4V was significantly greater than that of both HA-coated implants, (ii) HA coating enhanced early bone ingrowth into the porous surface of the implant, (iii) long-term fixation should depend on bone anchoring to this porous surface, and (iv) HA must be developed that does not obstruct the pores of the surface of the implant [166]. Souto et al. [167] examined HA-coated Ti-6Al-4V (which has a thickness between 50 and 200 μm and is very porous in nature) with EIS tests in Ringer's solution. It was found that (i) two-layer models describe the electrochemical behavior of the system by considering a porous film on the metallic substrate, (ii) metal dissolution occurs through the pores in the HA-coating, leading to the precipitation of salts which block the pores, and (iii) the resulting precipitates layer originates an additional barrier to metal dissolution in the system, as it can be followed through a significant increase in the resistance values measured after 20 days. It was also mentioned that after a 4-month exposure to Ringer's solution, no evidence was found from the EIS that might indicate a (partial) detachment of the HA film from the substrate, suggesting that the coated system may withstand longer exposure periods in this physiological solution [167].

The hydrothermal-electrochemical method is best suited for producing homogeneous AP coatings on electroconductive materials with complicated shape, such as the mesh. Yuda et al. [168] examined the effect of the AP coating prepared by this coating method on cell adhesion, proliferation, and differentiation of MC3T3-E1 cells in culture. The cells attached and spread well on the electrochemically deposited AP on titanium mesh. The number of cells that adhered on the deposited AP on titanium mesh was much greater than that on the surface without coating and that it also depended on the morphology of APs. When ALP activity as well as collagen and OC of the ECM were measured, the electrochemically AP-coated titanium mesh showed higher measurement values than the titanium mesh without coating. These results suggested that the AP-coated titanium mesh prepared by hydrothermal-electrochemical method has excellent biocompatibility [168].

A comparison study was conducted on the marginal bone loss (MBL), complications, and 12-year survival rates of CpTi and HA-coated implants placed in the maxilla. The sample group consisted of 120 patients (77 women and 43 men) treated from 1988 to 1997. A total of 388 implants (156 CpTi and 232 HA-coated) were placed in the maxilla. There were 126 (32.5%) immediate and 262 (67.5%) nonimmediate implants. Patients were evaluated annually. Mean follow-up was 60 ± 32.3 months. MBL was measured on radiographs using the implant threads as the dimensional reference. MBL, complications, and 12-year survival and success rates were correlated with implant coating, time of implantation, implant dimensions, and position in arch. It was reported that (i) total mean MBL was 1.07 mm, (ii) MBL was significantly lower with CpTi implants (0.55 mm) compared to HA-coated implants (1.51 mm), (iii) no statistical difference in regard to MBL was found between immediate and nonimmediate implants (0.86 vs. 1.16 mm), (iv) the total 12-year survival rate was 91.4%. HA-coated implants had a significantly higher 12-year survival rate than CpTi implants (93.2% vs. 89%), (v) nonimmediate implants had a significantly higher failure rate (8.2%) than the immediate implants (1.3%), and (vi) no correlation was found between type of implant coating and late implant failure. Based on these findings, it was concluded that HA-coated implants had greater MBL than CpTi implants but a higher 12-year survival rate, and immediate implants had a lower failure rate than the nonimmediate implants in this study population [169].

A porous metal coating applied to solid substrate implants has been shown, *in vivo*, to anchor implants by bone ingrowth. Calcium phosphate ceramics, in particular HA, are bioactive ceramics, which are known to be biocompatible and osteoconductive, and these ceramics deposited on to porous-coated devices may enhance bone ingrowth and implant fixation. Bi-feedstock of the titanium powder and composite ($\text{Na}_2\text{CO}_3/\text{HA}$) powder were simultaneously deposited on a Ti–6Al–4V substrate by a plasma sprayed method. At high temperature of plasma torch, the solid state of Na_2CO_3 would decompose to release CO_2 gas and then eject the molten Ti powder to induce the interconnected pores in the coatings. After cleaning and soaking in deionized water, the residual Na_2CO_3 in the coating would dissolve to form the open pores, and the HA would exist at the surface of pores in the inner coatings. By varying the particle size of the composite powder, the porosity of porous coating could be varied from 25.0% to 34.0%, and the average pore size of the porous coating could be varied to range between 158.5 and 202.0 μm . Using a standard adhesive test (ASTM C-633), the bonding strength of the coating was found between 27.3 and 38.2 MPa. By SEM, the HA was observed at the surfaces of inner pores in the porous coating. These results suggest that the method exhibits the potential to fabricate the bioactive ceramics onto porous-coated specimens to achieve bone ingrowth fixation for biomedical applications [170].

The osteointegration rate of titanium (TI) and duplex Ti plus HA (TH) coating systems with high surface roughness was investigated in healthy, aged, and estrogen-deficient sheep. After having evaluated the bone quality, both rods were implanted in the tibial diaphyses (two implants for each tibia) and epiphyses (1 implant for each tibia) of five young, five aged, and five aged and

ovariectomized sheep. It was reported that (i) the iliac crest trabecular bone volume and number in ovariectomized sheep were respectively 33.5% and 28.5% lower than in young sheep and lower than in the aged group, (ii) in the ovariectomized group the trabecular separation was 77.9% higher than in young and 30.9% higher than in aged animals, and (iii) lumbar vertebrae L5 bone mineral density was significantly lower in aged (8.9%) and ovariectomized sheep (19.3%) when compared with young animals. Five samples of five sheep from each group were analyzed for each observation. At 3 months, in cortical bone both affinity index and push-out test results showed no significant differences between the two materials in each group of animals. In trabecular bone, the affinity index of TH was significantly higher than that of TI in each group of animals (young: 90.7%; aged: 76.9%; ovariectomized: 49.9%) with no significant differences between groups. Based on these results, it was concluded that the performance of TI and TH surfaces was high not only in young, but also in ovariectomized animals and, therefore, they might be useful for aged and osteoporotic patients [171].

Lin et al. [172] evaluated the biologic effect *in vivo* of HA nanoparticle surface modification on CpTi or Ti–6Al–4V implants. Miniature cylindrical titanium and Ti–6Al–4V implants were pretreated with DAE, and a subset was further modified with HA nanoparticles using discrete crystalline deposition (DCD). Miniature implants of DAE titanium, DAE Ti–6Al–4V, DCD titanium, and DCD Ti–6Al–4V were surgically placed in the femora of rats. After 4 days, 1 week, and 2 weeks of healing, osteointegration was evaluated by implant push-in tests. Ti–6Al–4V samples were harvested at week 2 and prepared for nondecalcified histology and subjected to BIC measurement. It was reported that (i) DCD treatment generated a complex surface morphology via the bonded HA nanoparticles, (ii) however, the amplitude and spatial, hybrid, and functional surface roughness parameters measured at the micron and submicron levels did not depict topographic differences between the DAE and the DCD-modified implants, (iii) DAE titanium and DAE Ti–6Al–4V implants showed a sharp increase in push-in values at week 1, followed by a plateau at week 2, and (iv) DCD titanium and DCD Ti–6Al–4V implants showed similar sharp increases at week 1, but the push-in values continued to increase at week 2. It was concluded that DCD-derived surface modification with HA nanoparticles on titanium and Ti–6Al–4V implants resulted in progressive osteointegration profiles that were distinctively different from those of DAE controls and that early osteointegration may be more sensitively regulated by nanoscale surface characteristics [172]. Alzubaydi et al. [173] investigated the effect of the ceramic coatings (namely, HA and partially stabilized zirconia (PSZ)) on the bond strength between the bone and implant, and cell compatibility of screw-shaped Ti–6Al–7Nb dental implants. Electrophoretic deposition (EPD) technique was used to obtain a uniform coating of one of the three types of ceramic layers (HA, PSZ, and 50%HA + 50%PSZ) on the screws. The *in vivo* studies were performed by the implantation of screw-shaped uncoated and coated implants in the tibiae of white New Zealand rabbits. It was reported that (i) there was increased mechanical strength (torque value) at bone–implant interface with time, and the highest increment in the bond strength was recorded for implants coated with a

50% HA and 50% PSZ, (ii) histological results show that the coated Ti–6Al–7Nb screws after 18 weeks postimplantation seem to be well tolerated by the bone since no adverse tissue reaction was evident, (iii) however, there was a faster reaction of bone toward the coated implants compared to the uncoated one, and (iv) the histochemical stain studies show higher cellular activity and mature bone formation on all the samples [173].

The human osteoblast activity on thin HA-coated three-dimensional scaffolds made of titanium fiber web was evaluated [174]. A thin HA film was coated on a titanium fiber web by the molecular precursor method. Human osteoblasts were disseminated onto the uncoated and HA-coated titanium fiber web, and osteoblast activity was observed at days 3, 7, 14, and 21 of culture. It was reported that (i) proliferation activities of osteoblasts were significantly higher in the uncoated titanium fiber web, (ii) osteoblasts in the uncoated titanium fiber web showed a typical expression pattern, but those in the HA-coated titanium fiber web showed rapid OC expression and calcification at an early stage of culture, and (iii) OC expression per osteoblast was significantly higher in the HA-coated group. It was, therefore, concluded that HA coating with the molecular precursor method accelerated osteoblast functional activity [174].

Nanotechnology has been employed in attempts to enhance bone incorporation of dental implants. Often, nanoparticles are applied to the implant surface as particle coatings. However, the same properties that may increase the functionality may also lead to undiscovered negative effects, such as instability of nanocoating. Wennerberg et al. [175] investigated the stability/instability of the nanoparticles using a radiolabeling technique. Twenty threaded and turned titanium microimplants were inserted in 10 rats. All the 20 implants were coated with nanometer-sized HA particles. In order to trace the HA nanoparticles, the particles in 16 implants were labeled with calcium 45 (^{45}Ca). After 1, 2, 4, and 8 weeks, the implants and surrounding bone were retrieved and analyzed using autoradiography with respect to particle migration from the implant surface. Samples from the brain, liver, thymus, kidney, and blood, as well as wooden shavings from the rats' cages, were also retrieved and analyzed using liquid scintillation counting. It was found that (i) the radioactivity representing the localization of ^{45}Ca decreased over time from the vicinity of the implant, (ii) the amounts of ^{45}Ca found in the blood and in the rats' excretions decreased with time and corresponded well to each other, and (iii) after 8 weeks, the only trace of ^{45}Ca was found in the liver. It was concluded that released particles leave the body through the natural cleaning system, and the probability that the nanocoating will assemble in vital organs and thus become a potential biologic risk factor is unlikely [175].

Microcapsules containing active drugs, for example, an antimicrobial agent, with a HA shell are expected to prevent infection and to improve osteointegration simultaneously when used as implant materials. The effects of etching with HF were investigated to change the surface morphology of titanium in cases of adhesion of calcium-deficient HA microspheres onto titanium. The microspheres were mixed with HBSS to prepare slurry; the slurry was then put between two titanium disks that had been etched and kept soaking in Hank's solution for 7 days at 310 K. The coverage and

the degree of adherence of the microsphere were evaluated using electron probe microanalysis. It was found that (i) the etching with HF (concentration of 0.10 mol/L) caused the greatest adhesion and (ii) changing the temperature between 303 and 323 K showed a tendency for the degree of adherence to increase [176].

No options are available for local antibiotic delivery from uncemented implants. By loading porous titanium implant with a biomimetic HA coating with antibiotics, adequate local antibiotic concentrations can be obtained and infection susceptibility can be reduced. The efficacy of a tobramycin-loaded PA-coated titanium foam implant in preventing infection and the effects on osseointegration were studied. In 72 New Zealand White rabbits, an uncoated (Ti), PA-coated (PA), or Tobramycin-PA-coated (PA-tobra) titanium foam rod was implanted intramedullary in the left tibiae after contamination of the implant bed with none (control), 10^3 , 10^4 , or 10^5 CFU *Staphylococcus aureus*. PA-tobra implants were loaded with 2.4 mg tobramycin. After 28 days, analysis was done by bacteriology, histopathology, and histomorphometry. It was found that (i) 6% of the contaminated PA-tobra rabbits were infected, whereas this was 53% and 67% for PA and Ti, respectively, (ii) quantitative cultures were also significantly lower in the PA-tobra group, (iii) none of the control rabbits were infected, (iv) histopathological and histomorphometrical scores were both better for the PA-tobra group, although only significant compared to Ti, and (v) no significant differences were observed between PA and Ti rabbits. Based on these results, it was concluded that the application of tobramycin to PA-coated titanium foam implants appears to be an effective local antibiotic strategy for uncemented implants for infection prophylaxis and has a beneficial effect on implant fixation, which will result in improved long-term implant survival [177].

Adverse Effect

HA particles have long been suspected to disintegrate from implant surfaces, become entrapped in joint spaces of orthopedic bearing couples, and start a cascade leading to progressive polyethylene (PE) wear, increased osteolysis, and aseptic loosening. Stilling et al. [178] compared cup revision at 15 years' follow-up in a randomized group of patients with 26 cementless total hip arthroplasty (THA) components with titanium (Ti) versus first-generation HA coating, and also assessed radiographic PE wear and osteolysis to the 12-year follow-up or end point revision at a minimum of 5 years (mean, 10.9 years; range, 5–12.6 years). Two Ti-coated cups (17%) and eight HA-coated cups (57%) were revised at 15 years' follow-up. Femoral head penetration rate was 0.46 mm/year with the HA-coated cups and 0.38 mm/year with the Ti-coated cups; and a wide variance of linear wear with the HA-coated cups was observed. A positive association between high wear rate and revision, and between a high volume of osteolysis and revision, were also observed. These findings suggested inferior survival of medium-thickness spray-dried HA-coated cups with individual cases of excessive PE wear (which is, to some extent, related to wear debris toxicity due to biotribological action) and premature cup failure; these findings apply to first-generation modular cups and may not apply to other cup designs and new HA-coating technologies [178].

11.4.3 Ca-P and TCP Coating

Manufacturing Process

As we have just reviewed, the evidence showed the formation of an AP-like film containing Ca and P ions when Ti was pretreated in NaOH, followed by immersion in SBF or phosphate buffered liquid. Clinically, it was found that for Ti, an increase in oxide thickness and an incorporation of Ca and P were found in placed Ti implants which were in the shape of screws, and which had been osseointegrated in patients' jaws for times ranging from 0.5 to 8 years [179]. These provide "hindsight" knowledge; in other words, later on people will use this knowledge to modify the Ti surfaces. Formation of calcium phosphate on alkali- (10 M NaOH at 60°C for 24 h) and heat-treated (alkali-treated then heated at 600°C for 1 h followed by furnace cooling) CpTi was tested. Samples were immersed in the revised SBF with the same HCO_3^- concentration level as in human blood plasma. It was reported that (i) electron diffraction for the precipitates revealed that OCP, instead of HA, directly nucleates from amorphous calcium-phosphate, (ii) the OCP crystals continuously grew on the Ti surfaces rather than transforming to AP, and (iii) calcium titanate (CaTiO_3) was identified by electron diffraction [180]. Hanawa et al. [181] characterized surface films formed on titanium specimens which were immersed in electrolyte solutions (pH: 4.5, 5.1, 7.4) at 37°C for 1 h, 1 day, 30 days, and 60 days by XPS, Fourier transform infrared reflection absorption spectroscopy (FTIR-RAS) to understand the reaction between Ti and inorganic ions. For comparison, the surfaces of Ti-6Al-4V and NiTi were also characterized. XPS data revealed that calcium phosphates (Ca-P) were naturally formed on these specimens. In particular, compared with the CP formed on the Ti alloys, the CP formed on Ti immersed for 30 days in the solution with pH 7.4 was more like HA. It was also reported that (i) the compositions of the CP formed on the specimens changed with the immersion time and the pH value of the solution (the solution with pH 7.4 was Hank's balanced solution without organic species, solution with pH 4.5 was the artificial saliva without sodium sulfide and urea) and (ii) a CP similar to AP is naturally formed on Ti in a neutral electrolyte solution in 30 days [181].

The bioconductivity of a new biomedical Ti-29Nb-13Ta-6Zr alloy was achieved by a combination of surface oxidation and alkaline treatment [182]. It was reported that (i) immersion in a protein-free SBF and fast calcification solution led to the growth of CP phase on the oxidized and alkali-treated (10 M NaOH at 40°C for 24 h) alloy, and the new bioconductive surface was still harder than the substrate, (ii) oxidation at 400°C $\times$ 24 h led to the formation of a hard layer, (iii) the oxides are mainly composed of TiO_2 , with small amounts of Nb_2O_5 and ZrO_2 ; an oxygen diffusion layer exists beneath the surface oxide layer, and (iv) a titanate layer forms on the preoxidized surface after alkali treatment, and growth of a layer of Ca-P has been successfully induced on the titanate layer by immersing in SBF [182]. Bogdanski et al. [183] coated NiTi with CP by dipping in oversaturated CP solution. Since polymorphonuclear neutrophil (PMN) granulocytes belong to the first cells which will adhere to implant materials, the apoptosis of isolated

human PMN after cell culture on noncoated and CP-coated SME-NiTi was analyzed by light and SEM and flow cytometry. It was found that (i) in contrast to PMN adherent to noncoated TiNi, the apoptosis of PMN adherent CP-coated samples was inhibited and (ii) cell culture media obtained from cultured leukocytes with CP coating were able to transfer the apoptosis-inhibiting activities to freshly isolated PMN [183]. The compositions of the surface and the interface of calcium phosphate ceramic (CP) coatings electrophoretically deposited and sintered on CpTi and Ti–6Al–4V were evaluated before and after 4 weeks' immersion in a simulated physiological solution. At the CP coating–metal interface, it was mentioned that (i) the phosphorus diffused beyond the Ti oxide layer, resulting in the depleted phosphorus in the ceramic adjacent to the metal and (ii) the surface of the ceramic, however, was substantially unchanged [184].

The possible mechanisms of minimization of prosthesis-derived bone growth inhibitors by shielding of the metal and reduction of the associated metal dissolution was investigated by Ducheyne et al. [185]. Ti, Al, and V release rates were determined *in vitro* for Ti–6Al–4V alloy both with and without a CP coating. Surfaces were passivated in 40% HNO₃ at 55°C for 20 min. Calcium phosphate ceramic was electrophoretically deposited and subsequently vacuum sintered at 925°C for 2 h. Immersion for 1, 2, 4, 8, and 16 weeks in HBSS, simulated physiological solution with 1.5 mM DS-ethylenediamine tetraacetic acid (DS-EDTA). It was found that (i) the CP-coated specimens contained no measurable amounts of Ti, (ii) the Al ion solution around the CP-coated specimen was significantly greater than the concentration around the noncoated specimens; however, (iii) Al did not increase significantly with time, at least up to 4 weeks' immersion. The CP coating produced a significant increase of biological fixation, yet at the same time a greater Al release into solution, calling into question the value of calcium phosphate ceramic coating in shielding adverse metal passive dissolution to enhance bone growth [185].

Similarly to HA coating, there are various (chemical, electrochemical, and physical) processes for Ca-P coating available. The ions were implanted in sequence, first Ca and then P, both at a dose of 10^{17} ions/cm² at a beam energy of 25 keV on CpTi (grade II). The corrosion tests were done in SBF at 37°C. It was concluded that (i) the CpTi surface subjected to two-step implantation of Ca + P at a dose of 10^{17} ions/cm² becomes amorphous, (ii) the implantation of Ca + P ions increases the corrosion resistance in SBF exposure at 37°C for up to 3200 h, (iii) during exposures to SBF, CP precipitates from the implanted as well as nonimplanted samples, (iv) the CP precipitates have no effect on the corrosion resistance, and (v) under the conditions of the applied examination, the biocompatibility of Ti subjected to the two-step implantation of Ca + P ions was similar to that of an untreated sample [186]. CpTi (grade II) were surface-modified by anodic spark discharge anodization and a thin layer (ca. 5 μm) of amorphous TiO₂ containing Ca and P (Ti/AM). Some of the Ti/AM samples were further modified by hydrothermal treatment to produce a thin outermost (ca. 1 μm) of HA (Ti/AM/HA). It was reported that (i) nonanodized vacuum-annealed and hydrofluoric acid-etched samples, used as control material, showed good bone adsorption producing Ti excellent

surface properties, (ii) anodization at a voltage of 275 V that produced a crack-free amorphous TiO₂ film containing Ca and P (Ti/AM) provided good results for cytocompatibility and important morphological characteristics (micropores without crack development) but presented the lowest bone apposition, probably due to the degradation of amorphous TiO₂ film, and (iii) hydrothermal treatment at 300°C for 2 h that produced a submicrometer layer of HA crystals (ca. 1 µm) upon the amorphous TiO₂ film (Ti/AM/HA) gave rise to the highest bone apposition only at 8 weeks [187].

Coating by a RF magnetron sputter technique for the production of thin Ca–P coatings can be produced that vary in Ca/P ratio as well as structural appearance. Jansen et al. [188] studied the effect of noncoated titanium and three different Ca–P sputtered surfaces on the proliferation and differentiation (morphology and matrix production) of osteoblast-like cells. It was found that (i) proliferation of the osteoblast-like cells was significantly higher on noncoated than on Ca–P coated samples, (ii) on the other hand, more mineralized ECM was formed on the coated surfaces, and (iii) TEM confirmed that the cells on the coated substrates were surrounded by ECM with collagen fibers embedded in crystallized needle-shaped structures. On the basis of these findings, it was concluded that (i) the investigated Ca–P sputter coatings possess the capacity to activate the differentiation and expression of osteogenic cells and (ii) bone formation proceeds faster on Ca–P surfaces than on Ti substrates. Further, it was noticed that this bone stimulating effect appeared to be independent of the Ca–P ratio of the deposited coatings [188].

Hayakawa et al. [189] prepared four types of Ti implants: (1) as-blasted with titania (< 150 µm), (2) sintered with Ti beads with 50–150 µm diameter, (3) blasted with ion beam dynamic mixing (IBDM) Ca–P coating, and (4) multilayered sintered implants with IBDM Ca–P coating. The Ca–P coating was rapid heat-treated with infrared radiation at 700°C. The implants were inserted into the trabecular bone of the left and right femoral condyles of 16 rabbits, for 2, 3, 4, and 12 weeks. It was reported that (i) histological evaluation revealed new bone formation around different implant materials after already 3 weeks of implantation, (ii) after 12 weeks, mature trabecular bone surrounded all implants, and (iii) the combination of surface geometry and Ca–P coating benefits the implant–bone response during the healing phase [189].

Calcium phosphate (Ca–P) coatings have been applied onto titanium alloy prostheses to combine the strength of the metals with the bioactivity of Ca–P. It has been clearly shown in many publications that a Ca–P coating accelerates bone formation around the implant. However, longevity of the Ca–P coating for an optimal bone apposition onto the prosthesis remains controversial. Barrère et al. [190] evaluated biomimetic bone-like carbonate apatite (BCA) and OCP coatings which were deposited on Ti–6Al–4V samples to evaluate their *in vitro* and *in vivo* dissolution properties. The coated plates were soaked in α-MEM for 1, 2, and 4 weeks, and they were analyzed by backscattering electron microscopy (BSEM) and by FTIR. Identical coated plates were implanted subcutaneously in Wistar rats for similar periods. BSEM, FTIR, and histomorphometry were performed on the explants. *In vitro* and *in vivo*, a carbonate apatite (CA) formed onto OCP and BCA coatings via

a dissolution-precipitation process. It was reported that (i) *in vitro*, both coatings dissolved overtime, whereas *in vivo* BCA calcified and OCP partially dissolved after 1 week, and (ii) thereafter, OCP remained stable. This different *in vivo* behavior can be attributed to (1) different organic compounds that might prevent or enhance Ca-P dissolution, (2) a greater reactivity of OCP due to its large open structure, or (3) different thermodynamic stability between OCP and BCA phases. It was therefore concluded that these structural and compositional differences promote either the progressive loss or calcification of the Ca-P coating, and might lead to different osteointegration of coated implants [190]. Barrère et al. [191] studied also the nucleation and growth of a calcium phosphate (Ca-P) coating deposited on titanium implants from SBF, using AFM and ESEM. Forty titanium alloy plates were assigned into two groups: a smooth surface group having a maximum roughness $R_{\max} < 0.10 \mu\text{m}$ and a rough surface group with an $R_{\max} < 0.25 \mu\text{m}$. Titanium samples were immersed in SBF concentrated by five ($\text{SBF} \times 5$) from 10 min to 5 h and examined by AFM and ESEM. It was observed that scattered Ca-P deposits of approximately 15 nm in diameter appeared after only 10 min of immersion in $\text{SBF} \times 5$, and these Ca-P deposits grew up to 60–100 nm after 4 h on both smooth and rough Ti–6Al–4V substrates. It was found that (i) a continuous Ca-P film formed on titanium substrates, (ii) a direct contact between the Ca-P coating and the Ti–6Al–4V surface was observed, and (iii) the Ca-P coating was composed of nanosized deposits and of an interfacial glassy matrix, which might ensure the adhesion between the Ca-P coating and the Ti–6Al–4V substrate. The Ca-P coating detached from the smooth substrate, whereas the Ca-P film extended onto the whole rough titanium surface over time. In the case of rough Ti–6Al–4V, the Ca-P coating evenly covered the substrate after immersion in $\text{SBF} \times 5$ for 5 h. Accordingly, it was suggested that the heterogeneous nucleation of Ca-P on titanium was immediate and did not depend on the Ti–6Al–4V surface topography and the further growth and mechanical attachment of the final Ca-P coating strongly depended on the surface, for which a rough topography was beneficial [191].

Gan et al. [192] evaluated the interface shear strength of Ca-P thin films applied to Ti–6Al–4V substrates using a substrate straining method—a shear lag model. The Ca-P films were synthesized using sol–gel methods from either an inorganic or organic precursor solution. Strong interface bonding was demonstrated for both film types. It was reported that (i) the films were identified as nonstoichiometric HA, but with different Ca/P ratios, (ii) the Ca–P films were 1–1.5 μm thick, and (iii) the shear strength was approximately 347 and 280 MPa for inorganic and organic route-formed films, respectively [192]. NiTi was coated with CP by dipping in oversaturated CP solution, with layer thickness (5–20 μm). The porous nature of the layer makes it mechanically stable enough to withstand both the shape memory transition upon cooling and heating and also strong bending of materials (superelasticity). The adherence of human leukocytes and platelets to the AP layer was analyzed *in vivo*. By comparison to noncoated SME-NiTi, it was reported that leukocytes and platelets showed a significantly increased adhesion to the coated NiTi [193]. Fend et al. [194] pretreated CpTi by immersing in boiling $\text{Ca}(\text{OH})_2$

solution for 30–40 min to have only Ca-added precalcification, by immersing in 20% H_3PO_4 solution at 85–95°C for 30 min to have only P-added prephosphatization, and immersed these precalcified CpTi in supersaturated CP solution at 37°C for 1 week. It was found that (i) the osteoblast amount and activity on the surfaces containing Ca are higher than those on the surface containing sole P ions, (ii) Ca^{2+} ion sites on the material surfaces favor protein adsorption, such as fibronectin or vitronectin as ligands of osteoblast, onto the surface due to positive electricity, chemical, and biological function, and (iii) on the AP surfaces, Ca^{2+} ions are the active sites of the osteoblast adhesion and also promote the cell adhesion on PO_4^{3-} ion sites [194].

A self-assembled monolayer was formed in anhydrous pentane with 5% (v/v) 7-oct-1-enyltrichlorosilane, under argon atmosphere at 25°C for 1 h. CpTi foil was first oxidized in concentrated mixture of H_2SO_4 and H_2O_2 . A fast calcium phosphate deposition experiment was carried out by mixing Ca^{2+} and $(\text{PO}_4)^{3-}$ containing solution in the presence of the surface-modified Ti samples at pH 7.4 at room temperature in order to verify the nucleating abilities of these functional groups. Microanalytical results showed that poorly crystallized HA can be deposited on the self-assembled monolayer surfaces with $-\text{PO}_4\text{H}_2$ and $-\text{COOH}$ function groups but not onto the self-assembled monolayer with $-\text{CH}=\text{CH}_2$ and $-\text{OH}$; $-\text{PO}_4\text{H}_2$ exhibited a stronger nucleating ability than that of $-\text{COOH}$. The oxidized Ti sample also showed some CP deposition but to a lesser extent as compared to self-assembled monolayer surfaces. The predeposited HA can rapidly induce biomimetic AP layer formation after immersion in 1.5 SBF for 18 h regardless of the amount of predeposited HA. The results suggested that the predeposition of HA onto these functionalized self-assembled monolayer surfaces might be an effective and fast way to prepare biomimetic AP coatings on surgical implants [195]. Peng et al. [196] deposited electrochemically adherent and optically semitransparent thin calcium phosphate (Ca-P) films on titanium substrates in a modified SBF at 37°C. It was found that (i) coatings deposited by using periodic pulsed potentials showed better adhesion and better mechanical properties than coatings deposited with use of a constant potential, (ii) the coatings displayed a polydispersed porous structure with pores in the range of a few nanometers to 1 μm , and (iii) cell culture experiments showed that the Ca-P surfaces are nontoxic to MG63 osteoblastic cells *in vitro* and were able to support cell growth for up to 4 days, outperforming the untreated titanium surface in a direct comparison [196].

Zhang et al. [197] employed biomimetic deposition and electrochemical deposition in solution for CP deposition on sintered CpTi bead cylinders (1300°C for 2 h under vacuum). The supersaturated solution for CP deposition was prepared by dissolving NaCl , CaCl_2 , $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ in distilled water buffered to pH 7.4. Biomimetic deposition was done by immersing samples in solution at 37°C for 1, 2, 4, and 6 days, while electrochemical deposition was performed at -1.8 V (vs. $\text{Hg}_2\text{SO}_4/\text{Hg}$ reference) for 2 h at 37°C. It was reported that (i) a precoating alkaline treatment (5 mol/L NaOH at 60°C for 5 h) is necessary to obtain a uniform coating layer on the inner pore surfaces when the biomimetic deposition is used, (ii) electrochemical deposition is more efficient and less sensitive to the conditions of the

Ti surfaces compared to the biomimetic depositions; however (iii) the electrochemical deposition produces less uniform and thinner coating layers on the inner pore surfaces compared with the biomimetic deposition, and (iv) the crystal structure of the deposited Ca-P is OCP regardless of the deposition methods [197]. Heimann et al. [198] deposited HA and duplex HA + titania bond coat layers onto Ti-6Al-4V substrates by atmospheric plasma-spraying at moderate plasma enthalpies. From as-sprayed coatings and coatings incubated in SBF, electron-transparent samples were generated by focused ion beam excavation. It was found that (i) adjacent to the metal surface a thin layer of amorphous calcium phosphate (CP) was deposited, (ii) after *in vitro* incubation of duplex coatings for 24 weeks, Ca-deficient defect AP needles precipitated from amorphous CP, and (iii) during incubation of HA without a bond coat for 1 week, diffusion bands were formed within the amorphous CP of 1–2 μm width parallel to the interface metal/coating, presumably by a dissolution-precipitation sequence [198]. Aluminoborosilicate glass + HA powder were coated on CpTi at 800–900°C. It was found that (i) the precipitates were Ca-deficient carbonate with low crystallinity, (ii) both morphologies and composition of the precipitates *in vivo* were similar to those *in vitro*, and (iii) the HA particles on the surface of the composite act as nucleation sites for precipitation in physiologic environments, whereas the glass matrix is independent of it [199].

For the same purpose as for the HA-coating, a Ca-P coated layer is needed for postcoating heat treatment. Lucas and Ong [200] investigated the postdeposition heat treatments of ion beam as-sputtered coatings by varying the time and temperature. Ca-P coatings, deposited using a HA-fluorapatite target, received the postdeposition heat treatments as follows: 150°C, 300°C, 400°C, 500°C, and 600°C for either 30 min or 60 min, followed by furnace cooling to room temperature. It was found that (i) the average bond strengths for the coatings heated to 500°C (30 min), 600°C (30 min), and 600°C (1 h) were 40.1, 13.8, and 9.1 MPa, respectively, (ii) the 500°C heat treatment for 30 min resulted in a HA-type coating without reducing the tensile bond strength of the coating, and (iii) thus, temperature and time are critical parameters in optimizing coating properties [200], suggesting that the diffusion process must be significantly involved.

As we have seen above, there is much evidence indicating that, in *in vitro* tests, calcium phosphate is precipitated on such surfaces when they are immersed in a simulated physiological solution, suggesting a main reason for excellent biocompatibility [165]. On the other hand, there is evidence suggesting that, *in vivo*, after even 7-day implantation of such modified Ti in rat bone, it was found that Ca/P ratio was reduced by less than 1 (i.e., Ca-depletion) [201]. With an electron-beam evaporation process, a calcium phosphate (Ca-P) thin film of ~500 nm thick was deposited on sandblasted with large grits and acid-etched (SBA) Ti without changing the typical morphology of the SBA surface. Dissolution behavior was investigated by measuring the amount of dissolved phosphate ions with ion chromatography after immersing the SBA Ti sample coated with a Ca-P film in 1 mL deionized water maintained at 37°C for different periods of soaking time, and the surface morphology was observed with field-emission SEM. The amount of phosphate ions increased quickly right after immersion but began to decrease after

2 days of immersion by redeposition with Ca ions as AP, and the amount of biometric AP increased with the extended soaking time. The SaOS-2 cell was more attached on the coated surface, and the *in vivo* evaluation was that the Ca-P deposited SBA implant greatly improved the new bone formation ability [202].

Mechanical compatibility between a coating and a substrate is important for the longevity of implant materials. While previous studies have utilized the entire coating for analysis of mechanical compatibility of the surface, it was focused on the nanoindentation of a uniformly thermal sprayed splat. HA was thermally sprayed to create a homogeneous deposit density, as confirmed by micro-Raman spectroscopy, of amorphous calcium phosphate. Substrates were CpTi, Ti-6Al-4V, Co-Cr alloy, and stainless steel. Nanoindentation revealed that splats deposited on the different metals have similar hardness and elastic modulus values of 4.2 and 80 GPa, respectively. The mechanical properties were affected by the substrate type more than residual stresses, which were found to be low. It is recommended that amorphous calcium phosphate is annealed to relieve the quenching stress or that appropriate temperature histories are chosen to relax the stress created in cooling the coating assembly [203].

Clinical Evaluation

Yang et al. [204] investigated and compared bone formation on titanium implant surfaces coated with biomimetically deposited calcium phosphate (BDCa-P) or electrochemically deposited HA (EDHA). The implants were separated into three groups: a control group, a BDCa-P group, and an EDHA group. Surface analysis was performed by field-emission SEM, XRD, and FTIR. Implants were inserted in a randomized arrangement into rabbit tibiae. After 2, 4, and 8 weeks, the tibiae were retrieved and prepared for histomorphometric evaluation. It was found that (i) field-emission SEM revealed that the BDCa-P crystals were flakelike and the EDHA crystals were rodlike with a hexagonal cross section, (ii) XRD patterns and FTIR spectra showed that the BDCa-P coating consisted of HA and OCP, whereas the EDHA coating consisted of HA, (iii) histologic observation showed that new bone on the EDHA-coated implant became mature after 4 weeks, while new bone on the control and BDCa-P-coated implants was mature after 8 weeks, (iv) the EDHA implant showed significantly greater BIC and BA compared to the control and BDCa-P implants during 4–8 weeks, and (v) the BDCa-P coating failed to show increased bone formation during the test period. Based on these findings, it was concluded that the present EDHA coating has good bone formation properties [204].

Osteointegration of a novel calcium phosphate (Ca-P)-coated titanium porous oxide implant surface was evaluated [205]. Twenty adult male New Zealand White rabbits were used. Each animal received two titanium porous oxide-surfaced implants (benchmark control: TiUnite, Nobel Biocare) and two novel Ca-P-coated titanium porous oxide-surfaces implants; they were allocated to contralateral tibia implant sites. The animals were sacrificed after 2 or 4 weeks, and tissues were evaluated histometrically. It was found that (i) healing was generally uneventful,

(ii) a removal torque analysis showed significantly higher peak values for the control implants than for the test implants at 2 weeks (31.4 N-cm vs. 20.4 N-cm) and 4 weeks (48.4 N-cm vs. 30.3 N-cm), (iii) light microscopy showed no significant differences in local bone density around control and test implants at 2 and 4 weeks (range, 85–91% within the thread area and 91–95% immediately outside the threads), and (iv) at 2 weeks, bone–implant contact for control and test implants averaged 81.8% and 75.7%, respectively, and at 4 weeks the bone–implant contact values were 79.4% and 73.5%, respectively. Based on these results, it was concluded that the novel Ca-P-coated surface effectively supports osteointegration [205].

Surface modification of titanium implants to improve their fixation in bone tissue is of great interest. A novel approach to enhance implant performance by applying important principles of bone mineralization to biomedical coatings was discussed [206]. As an attempt to mimic the biphasic biomineralization process, both the enzyme ALP and calcium phosphate (Ca-P) were immobilized onto Ti disks, thereby triggering enzymatically and physicochemically controlled biomineralization pathways. ALP, Ca-P and ALP–Ca-P composite coatings with preserved functionality of ALP were successfully deposited using electrospray deposition. *In vitro* soaking studies in cell culture medium revealed that crystal growth initially proceeded at a faster rate on Ca-P-coated Ti than on ALP-containing coatings, but mineral deposition onto ALP-coated Ti caught up with the calcification behavior of Ca-P coatings upon long-term soaking. Cell culture experiments with osteoblast-like cells, however, demonstrated the opposite effect in mineral deposition on the electrosprayed Ca-P and ALP coatings. The ALP–Ca-P composite coatings showed delayed proliferation as well as accelerated mineralization in comparison to cells cultured on the Ca-P-coated and uncoated Ti. In conclusion, it was mentioned that the osteogenic potential of Ti can be stimulated by ALP-containing coatings [206].

Murai et al. [207] evaluated the effects of different sizes of β -TCP particles on bone augmentation within a titanium cap. In 20 rabbits, the calvarium was exposed and a circular groove was prepared. After marrow penetration, a standardized hemispherical titanium cap was placed in the circular groove. The cap was filled with small-sized (100–250 μm) or medium-sized (250–500 μm) β -TCP particles for the experimental site and without β -TCP for the control site. After 1 and 3 months of healing, the animals were euthanized and examined histologically. It was reported that (i) there was a statistically significant difference in the amount of mineralized bone generated between the experimental and control groups in the 3-month specimens and (ii) furthermore, the medium-sized particles showed significantly more mineralized bone than did the small-sized particles. Based on these findings, it was suggested that β -TCP might be effective for bone formation and that medium-sized particles are more useful than small-sized particles in bone maturation [207].

Bioactive silica-calcium phosphate nanocomposite (SCPC) has been coated on Ti–6Al–4V implant employing an EPD technique. The effects of composition and pH of the suspending medium on the zeta potential of three different SCPC formulations—SCPC25, SCPC50, and SCPC75—were analyzed. The average zeta potential of SCPC50 in pure ethanol was more negative than that of SCPC25 or SCPC75; however, the difference was not statistically significant. Disks of

Ti–6Al–4V were passivated, coated with SCPC50 (200 nm–10 μ m), and thermally treated at 600–800°C to produce a coating thickness in the range of 30.1–43.1 μ m. After treatment at 600°C, 700°C, and 800°C, the adhesion strength at the SCPC50/Ti–6Al–4V interface was 42.6, 44.7, and 47.2 MPa, respectively. SEM–EDX analyses of SCPC50-coated Ti–6Al–4V preimmersed in phosphate-buffered saline (PBS) for 7 days showed the formation of a Ca-deficient HA surface layer. Bone marrow mesenchymal stem cells (bMSCs) attached to the SCPC50-coated implants expressed significantly higher ALP activity (82.4 nmol p-NP/mg protein/min) than that expressed by cells attached to HA-coated or uncoated implants. Results of the study indicate that bioactive SCPC50 can efficiently be coated on Ti–6Al–4V using EPD and the SCPC50 coating has the potential to enhance bone integration with the orthopedic implant [208].

11.4.4 Composite Coating

Manufacturing Process and Characterization

Ng et al. [209] mimicked biomineralization of bone by applying an initial TiO₂ coating on Ti–6Al–4V by electrochemical anodization in two dissimilar electrolytes, followed by the secondary calcium (Ca-P) coating, subsequently applied by immersing the substrates in a SBF with three times concentration (SBF $\times$ 3). EIS and DC potentiodynamic polarization assessments in SBF revealed that the anodic TiO₂ layer is compact, exhibiting up to a fourfold improvement in *in vitro* corrosion resistance over unanodized Ti–6Al–4V. XPS analysis indicates that the anodic Ti oxide is thicker than air-formed ones with a mixture of TiO_{2-x} compound between TiO₂ and Ti interfaces. The morphology of the dense Ca-P film formed, when observed using SEM, is made up of linked globules 0.1–0.5 μ m in diameter without observable delamination. It was also found that (i) the calculated Ca:P ratios of all samples (1.14–1.28) are lower than stoichiometric HA (1.67), and (ii) a duplex coating consisting of a compact TiO₂ with enhanced *in vitro* corrosion resistance and bone-like AP coating can be applied on Ti–6Al–4V by anodization and subsequent immersion in SBF [209].

Knabe et al. [210] investigated the effects of novel calcium-titanium, calcium, titanium-zirconium phosphates suitable for plasma-spraying on CpTi substrate on the expression of bone-related genes and proteins of human bone-derived cells and compared the effects to that on native Ti and HA-coated Ti. Test materials were acid-etched and sandblasted, PSHA, and sintered CaPO₄ with Ti, Zr, TiO₂, and ZrO₂. Human bone-derived cells were grown on these surfaces for 3, 7, 14, and 21 days, counted, and probed for various mRNAs and proteins. It was reported that (i) all substrates significantly affected cellular growth and the temporal expression of an array of bone-related genes and proteins, (ii) at 14 and 21 days, cells on sintered titanium surfaces displayed significantly enhanced expression of all osteogenic mRNAs, and (iii) surfaces of 55CaO $\cdot$ 20TiO₂ $\cdot$ 31P₂O₅ and CaTi₄(PO₄)₆ sintered titanium had the most effect on osteoblastic differentiation inducing a greater expression on an array of osteogenic markers than recorded for cells

grown on HA, suggesting that these novel sintered materials may possess a higher potency to enhance osteogenesis [210].

Bioactive calcium phosphate (Ca-P) coatings were produced on titanium by using phosphate-based glass (P-glass) and HA, and their feasibility for hard tissue applications was addressed *in vitro* by Kim et al. [211]. P-glass and HA composite slurries were coated on Ti under mild heat treatment conditions to form a porous thick layer, and then the micropores were filled in with a HA sol–gel precursor to produce a dense layer. The resultant coating product was composed of HA and calcium phosphate glass ceramics, such as TCP and calcium pyrophosphate (CPP). It was reported that (i) the coating layer had a thickness of approximately 30–40 μm and adhered to the Ti substrate tightly, (ii) the adhesion strength of the coating layer on Ti was as high as about 30 MPa, (iii) the human osteoblastic cells cultured on the coatings produced by the combined method attached and proliferated favorably, and (iv) the cells on the coatings expressed significantly higher ALP activity than those on pure Ti, suggesting the stimulation of the osteoblastic activity on the coatings [211]. Yamada et al. [212] utilized the Cullet method for which (1) the mixture of HA powder and glass frits are sintered at 900–1000°C for 5–10 min to prepare well-homogenized coating powder, whereas the conventional method is just mixing and not sintering and (2) the time of etching treatment, through which the bioactive surface is formed using the mixed solution of HNO_3 and HF, is relatively short (within 1 min) compared to the conventional method. Through this method, it was reported that functionally gradient HA/Ti composite implants were successfully fabricated with higher quality compared with the conventional method [212]. Maxian et al. [213] evaluated the effect of amorphous calcium phosphate and polycrystallized (60% crystalline) HA coatings on bone fixation of smooth and rough (Ti–6Al–4V powder sprayed) Ti–6Al–4V implants after 4 and 12 weeks of implantation in a rabbit transcortical femoral model. Histological evaluation of amorphous versus poorly crystallized HA coatings showed significant differences in bone apposition and coating resorption that were increased within cortical compared to cancellous bone. The poorly crystallized HA coatings showed the most degradation and least bone apposition. Mechanical evaluation, however, showed no significant differences in push-out shear strengths. Significant enhancement in interfacial shear strengths for bioceramic coated, as compared to uncoated implants, was seen for smooth-surfaced implants (3.5–5 times greater) but not for rough-surfaced implants at 4 and 12 weeks. Based on these results, it was suggested that once early osteointegration is achieved, biodegradation of a bioactive coating should not be detrimental to the bone/coating/implant fixation [213]. PSHA coatings on titanium alloy substrates have been used extensively due to their excellent biocompatibility and osteoconductivity. However, the erratic bond strength between HA and Ti alloy has raised concern over the long-term reliability of the implant. Accordingly, Khor et al. [214] developed HA/yttria-stabilized-zirconia (YSZ)/Ti–6Al–4V composite coatings that possess superior mechanical properties to conventional PSHA coatings. Ti–6Al–4V powders coated with fine YSZ and HA particles were prepared through a unique ceramic slurry mixing method. The composite powder was employed as feedstock for plasma-spraying of the

HA/YSZ/Ti–6Al–4V coatings. The influences of net plasma energy, plasma spray standoff distance, postspray heat treatment on microstructure, phase composition, and mechanical properties were investigated. It was found that (i) coatings prepared with the optimum plasma sprayed condition showed a well-defined splat structure, (ii) HA/YSZ/Ti–6Al–4V solid solution was formed during plasma-spraying, which was beneficial for the improvement of mechanical properties, (iii) the microhardness, MOE, fracture toughness, and bond strength increased significantly with the addition of YSZ, and (iv) postspray heat treatment at 600°C and 700°C for up to 12 h was found to further improve the mechanical properties of coatings [214]. YSZ is often used as reinforcement for many ceramics because it has the merits of high strength and enhanced toughening characteristics during crack–particle interactions [215–218].

HA coatings with titania addition were produced by the high-velocity oxy-fuel spray process. It was found that (i) the addition of TiO₂ improves the MOE, fracture toughness, and shear strength of high-velocity oxy-fuel sprayed HA-based coatings, (ii) the incorporation of the secondary titania phase is found to have a negative effect on the adhesive strength of high-velocity oxy-fuel–sprayed HA coatings, (iii) the titania is found to inhibit the decomposition of HA at elevated temperatures lower than 1410°C, at which point the mutual chemical reaction occurs, and (iv) a small amount of TiO₂ added into high velocity oxy-fuel–sprayed HA coatings with less than 20 vol.% is, therefore, recommended for strengthening of HA coatings. Li et al. [219] fabricated a two-layer HA/HA + TiO₂ bond coat composite coating (HTH coating) on titanium by the plasma-spraying technique. The HA + TiO₂ bond coat (HTBC) consists of 50 vol.% HA and 50 vol.% TiO₂ (HT). The as-sprayed HT coating consists mainly of crystalline HA, rutile TiO₂, and amorphous Ca-P phase, but the postspray heat treatment at 650°C for 120 min effectively restores the structural integrity of HA by transforming non-HA phases into HA. It was found that there exists interdiffusion of the elements within the HTBC, but no chemical product between HA and TiO₂, such as CaTiO₃, was formed. The toughening and strengthening mechanism of HTBC is mainly due to TiO₂ as obstacles resisting cracking and the reduction of the near-tip stresses resulting from stress-induced microcracking [219]. TiO₂ coatings were prepared on NiTi alloy by heat treatment in air at 300°C, 400°C, 600°C, and 800°C. The heat-treated NiTi alloy was subsequently immersed in a SBF for the biomimetic deposition of the AP layer onto the surface of TiO₂ coating. The AP coatings, as well as the surface oxide layer on NiTi alloy, were microanalytically characterized by Gu et al. [220]. Results showed the samples heat-treated at 600°C produced a layer of anatase and rutile TiO₂ on the surface of NiTi. It was a surprise to find that no TiO₂ was detected on the surface of NiTi after heat treatment at 300°C and 400°C by XRD, while rutile was formed on the surface of the 800°C heat-treated sample. It was found that the 600°C heat-treated NiTi induced a layer consisting of microcrystalline carbonate containing HA on its surface most effectively, while 300°C and 400°C heat-treated NiTi did not form AP. This was due to the presence of anatase and/or rutile in the 600°C and 800°C heat-treated NiTi, which could provide atomic arrangements in their

crystal structures suitable for the epitaxy of AP crystals, and anatase had better AP-forming ability than rutile. XPS and Raman results revealed that this AP layer was a carbonated and nonstoichiometric AP with Ca/P ratio of 1.53, which was similar to the human bone. It was mentioned that the formation of AP on 600°C heat-treated NiTi following immersion in SBF for 3 days indicated that the surface-modified NiTi possessed excellent bioactivity [220].

Van Walter et al. [221] introduced a porous composite material, named “Ecopore,” and described *in vitro* investigation of the material and its modification with fibronectin. The material is a sintered compound of rutile TiO_2 and the volcanic silicate perlite with a macrostructure of interconnecting pores. In an *in vitro* model, human primary osteoblasts were cultured directly on Ecopore. It was reported that human osteoblasts grew on the composite as well as on samples of its single constituents, TiO_2 and perlite glass, and remained vital, but cellular spreading was less than on tissue culture plastic. To enhance cellular attachment and growth, the surface of the composite was modified by etching, functionalization with aminosilane, and coupling of fibronectin, resulting in greatly enhanced spreading of human osteoblasts. It was, therefore, concluded that (i) Ecopore is nontoxic and sustains human osteoblasts growth, cellular spreading being improvable by coating with fibronectin and (ii) the composite may be usable in the field of bone substitution [221].

Shtansky et al. [222] performed a comparative investigation of multicomponent thin films based on the systems Ti–Ca–C–O–(N), Ti–Zr–C–O–(N), Ti–Si–Zr–O–(N), and Ti–Nb–C–(N). $\text{TiC}_{0.5} + 10\%\text{CaO}$, $\text{TiC}_{0.5} + 20\%\text{CaO}$, $\text{TiC}_{0.5} + 10\%\text{ZrO}_2$, $\text{TiC}_{0.5} + 20\%\text{ZrO}_2$, $\text{Ti}_5\text{Si}_3 + 10\%\text{ZrO}_2$, $\text{TiC}_{0.5} + 10\%\text{Nb}_2\text{C}$, and $\text{TiC}_{0.5} + 30\%\text{Nb}_2\text{C}$ composite targets were manufactured by means of self-propagating high-temperature synthesis, followed by DC magnetron sputtering in an atmosphere of argon or in a gaseous mixture of argon and nitrogen. The biocompatibility of the films was evaluated by both *in vitro* and *in vivo* experiments. *In vitro* studies involved the investigation of the proliferation of (RAT-1) fibroblasts cells and (IAR-2) epithelial cells on the tested films, morphometric analysis, and actin cytoskeleton staining of the cells cultivated on the films. *In vivo* studies were fulfilled by subcutaneous implantation of Teflon plates coated with the tested films in mice and analysis of the population of cells on the surfaces. It was reported that (i) the films showed high hardness in the range of 30–37 GPa, significantly reduced MOE, low friction coefficient down to 0.1–0.2, and low wear rate in comparison with conventional magnetron-sputtered TiC and TiN films, (ii) no statistically significant differences in the attachment, spreading, and cell shape of cultured both cells on the Ti–Ca–C–O–(N), Ti–Zr–C–O–(N) ($\text{TiC}_{0.5} + 10\%\text{ZrO}_2$ target), Ti–Si–Zr–O–(N) films, and the uncoated substrata were detected, and (iii) the adhesion and proliferation of cultured cells *in vitro* was perfect on all the investigated films. Based on these findings, it was concluded that the combination of excellent mechanical properties with nontoxicity and biocompatibility makes Ti–Ca–C–O–N, Ti–Zr–C–O–N, and Ti–Si–Zr–O–N films promising candidates as tribological coatings to be used for various medical applications like total joint prostheses and dental implants [222].

Chu et al. [223] characterized microanalytically a bioactive sodium titanate/titania graded film formed *in situ* on NiTi-shaped memory alloy by oxidizing in H_2O_2 solution and subsequent NaOH treatment. The bioactivity of the film was investigated using a SBF soaking test. A titania (TiO_2) layer was first found on NiTi substrate after it was oxidized in H_2O_2 solution, and then a porous sodium titanate (Na_2TiO_3)/titania film with many Ti—OH groups, and a trace of Ni_2O_3 was formed by the reaction of partial TiO_2 phase with NaOH solution. After immersion in SBF for 12 h, AP was observed to nucleate and grow on the film. By prolonging the soaking time, more AP appeared on its surface. Moreover, XPS depth profiles of O, Ni, Ti, and Na show that the bioactive film possesses a smooth-graded interface structure to NiTi substrate, which is in favor of sufficient mechanical stability of AP layer by subsequent deposition in SBF [223].

Composites with Collagen or CHI

Redepenning et al. [224] prepared another type of biocomposite coating containing brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) and CHI by electrochemical deposition. The brushite/CHI composites were converted to HA/CHI composites in aqueous solutions of sodium hydroxide. The coatings ranged from about 1–15% CHI by weight. It was mentioned that qualitative assessment of the coatings showed adhesion significantly improved over that observed for electrodeposited coatings of pure HA [224]. Different biomaterials have been used as scaffolds for bone tissue engineering. Rodrigues et al. [225] characterized biomaterial composed of sintered (at 1100°C) and powdered HA and type I collagen (both of bovine origin) designs for osteoconductive and osteoinductive scaffolds. Collagen/HA proportions were 1/2.6 and 1/1 by weight, with particle sizes ranging from 200 to $400\text{ }\mu\text{m}$. XRD and infrared spectroscopy showed that the sintered (1100°C) bone was composed essentially of HA with minimum additional groups as surface calcium hydroxide, surface and crystal water, free carbon dioxide, and possibly brushite. It was reported that osteoblasts adhered and spread on both the HA particle surface and the collagen fibers, which seemed to guide cells between adjacent particles [225], suggesting that this biocomposite can be considered as ideal for its use as scaffold for osteoconduction and osteoinduction. Cheng et al. [226] prepared electrochemically a bovine serum albumin (BSA) protein containing AP coating on a HA-coated Ti—6Al—4V. It was reported that (i) the method resulted in a 70-fold increase in BSA inclusion compared to simple adsorption and was subsequently released by a slow mechanism (15% loss over 70 h) and (ii) thus, this technique provides an efficient method of protein incorporation at physiological stem, with a potential for sustained release of therapeutic agents, as may be required for metallic implant fixation [226].

11.4.5 TiN and TiC Coating

Mechanical—electrochemical interactions accelerate corrosion in mixed-metal modular hip prostheses. These interactions can be reduced by improving the modular component machining tolerances or by improving the resistance of the components

to scratch or fretting damage. Wrought Co-alloy (Co–Cr–Mo) is known to have better tribological properties compared to the Ti–6Al–4V alloy. Thus, improving the tribological properties of this mixed-metal interface should center on improving the tribological properties of Ti–6Al–4V. It was mentioned that (i) the nitrogen-diffusion–hardened Ti alloy samples had a more pronounced grain structure, more nodular surface, and significantly higher mean roughness values than the control Ti–6Al–4V, (ii) the nitrided Ti–6Al–4V samples also exhibited at least equivalent corrosion behavior and a definite increase in surface hardness compared to the control Ti–6Al–4V samples, and (iii) fretting can be reduced by decreasing micromotion or by improving the tribological properties (wear resistance and surface hardness) of the material components at this interface [227]. The corrosion behavior of the titanium nitride-coated TiNi alloy was examined in 0.9% NaCl solution by potentiodynamic polarization measurements and a polarization resistance method [228]. XPS spectra showed that the titanium nitride film consisted of three layers: a top layer of TiO_2 , a middle layer of TiN_x ($x > 1$), and an inner layer of TiN, which agreed very well with results obtained by Oshida and Hashem [229]. The passive current density for the titanium nitride-coated alloy was approximately two orders of magnitude lower than that of the polished alloy in the potential range from the free corrosion potential to +500 mV (vs. Ag/AgCl). Pitting corrosion associated with breakdown of the coated film occurred above this potential. The polarization resistance data also indicated that the corrosion rate of the titanium nitride-coated alloy at the corrosion potential (+50 to +100 mV) was more than one order of magnitude lower than that for the polished alloy. It was concluded that the corrosion rate of TiNi alloy can be reduced by more than one order of magnitude by titanium nitride coating, unless the alloy is highly polarized anodically *in vivo* [228]. Ti–6Al–7Nb alloy was treated at 70 and 100 keV energy using a 150 keV accelerator at different doses between 1×10^{16} and 3×10^{17} ions/cm², and was corrosion-tested in Ringer's solution. It was reported that nitrogen ion implantation enhanced the possibility of passivation and reduced the corrosion kinetics of the alloy surface with increasing tendency for repassivation [230]. Bordji et al. [231] prepared Ti alloys treated by (1) glow discharge nitrogen implantation (10^{17} atoms cm⁻²), (2) plasma nitriding by plasma diffusion treatment, and (3) deposition of TiN layer by plasma-assisted chemical vapor deposition (PACVD) additionally to plasma diffusion treatment. A considerable improvement was noticed in surface hardness, especially after the two nitriding processes. A cell culture model using human cells was chosen to study the effect of such treatments on the cytocompatibility. The results showed that Ti–5Al–2.5Fe alloy was as cytocompatible as the Ti–6Al–4V alloy, and the same surface treatment led to identical biological consequences on both alloys. It was concluded that (i) after the two nitriding treatments, cell proliferation and viability appeared to be significantly reduced and the SEM revealed somewhat irregular surface states; however (ii) osteoblast phenotype expression and protein synthesis capability were not affected [231]. Goldberg and Gilbert [232] utilized the plasma vapor deposition (PVD) technique, by which the samples were placed into a vacuum chamber and sputtered to remove the oxide film, followed by depositing a 200 nm thick

interlayer of titanium to enhance the coating/substrate interface. Alternating layers of TiN and AlN were deposited until a coating thickness of approximately 5 μm was produced. The mechanical and electrochemical behavior of the surface oxides of Co–Cr–Mo and Ti–6Al–4V alloys during fracture and repassivation play an important role in the corrosion of the taper interfaces of modular hip implants. These corrosion properties were investigated in one group of Co–Cr–Mo and Ti–6Al–4V alloy samples passivated with nitric acid and another group coated with TiN/AlN coating. It was found that (i) Co–Cr–Mo had a stronger surface oxide and higher interfacial adhesion strength, making it more resistant to fracture than Ti–6Al–4V, (ii) if undistributed, the oxide on the surface of Ti–6Al–4V significantly reduced dissolution currents at a wider range of potential than Co–Cr–Mo, making Ti–6Al–4V more resistant to corrosion, and (iii) the TiN/AlN coating had higher hardness and MOE than Co–Cr–Mo and Ti–6Al–4V [232].

In spite of their high strength, low density, and good corrosion resistance, the usefulness of Ti alloys in general engineering components is frequently limited by their poor wear resistance. If the alloy surface is subjected to conditions of sliding or fretting, adhesive wear can rapidly lead to catastrophic failure unless appropriate surface engineering is carried out. In order to combat modest contact loads, several surface treatments are commercially available, such as plasma nitriding or PVD coating with TiN. Titanium nitride is known for its high surface hardness and mechanical strength. It was also reported that the dissolution of Ti ions is very low [233]. As for dental implants, they are composed of various components. The implant abutment part (the mucosa penetration part) is exposed in the oral cavity, and so plaque and dental calculus easily adhere to it. Removal of the plaque and dental calculus is necessary to obtain a good prognosis throughout the long-term maintenance of the implant. Based on this background, Kokubo et al. [234] prepared CpTi (grade I) samples by polishing with #2000 grit paper, or buff-polishing with 6 μm diamond emulsion paste, followed by a 0.1% HF acid solution for 10 s to clean the surface, then treated in N_2 atmosphere of 1 atm at 850°C for 7 h (N_2 flow rate: 50 L/min). It was reported that (i) the nitrided layer about 2 μm thick composed of TiN and Ti_2N was formed on Ti by a gas nitriding method, and the dissolved amount of Ti ion in SBF³ was as low as the detectable limit of inductively coupled plasma mass spectroscopy (ICP-MS), and that the 1% lactic acid showed no significant difference from Ti [234].

The majority of surface treatments such as plasma nitriding or PVD coating with TiN are, however, carried out in the solid state and the depth of coating or hardening is restricted by low diffusivity. The diffusion coefficient of nitrogen in Ti is more than a thousand times slower than that in steels due to different crystal-line structures. The packing factor of Ti (hexagonal closed-packed (HCP) (crystal structure)) is 74%, while that of steel (body-centered cubic (BCC) (crystal structure)) is 68%, so that steel has more spaces available for diffusing species. In order to achieve the depth of hardening necessary to withstand the subsurface Hertzian

³ SBF: Na^+ (142.0), K^+ (5.0), Mg^{2+} (1.5), Ca^{2+} (2.5), Cl^- (148.8), HCO_3^- (4.2), HCO_4^- (1.0). H.P. Na (142.0), K (5.0), Mg (1.5), Ca (2.5), Cl (103.0), HCO_3 (13.5), HPO_4 (1.0) (by wt%).

stresses induced by heavy rolling contact, it is necessary to alloy the Ti surface in the molten state. The necessary depth of surface hardening can readily be achieved in this way by laser-melting the surface in the presence of interstitial alloying elements such as carbon, oxygen, and nitrogen. Of these, nitrogen has been found to provide the best balance between increased hardness and decreased ductility and can easily be added by laser gas nitriding. The Hertzian compressive stress in the substrate was increased to 1.36 GPa [235]. Pure iron has allotropic phase transformations: the first one is 910°C between α -BCC and γ -face-centered cubic (FCC) (crystal structure), and the second one is 1390°C between γ -FCC and δ -BCC. While investigating the deformation mechanism of transformation superplasticity, Oshida observed that the transformation front behaves as if semiliquid due to losing a clear crystalline electron diffraction pattern even though both α -BCC and γ -FCC are still in solid state. Based on this finding, the “quasi-liquid transformation front” model was proposed. As mentioned in Chapter 10, one of various applications using transformation superplasticity is a nitridation of metallic materials if they have an allotropic phase transformation temperature. It was demonstrated that CpTi was successfully nitrided when CpTi was heated and cooled repeatedly, passing the β -transus temperature (between 800°C and 930°C), several times in a nitrogen gas-filled chamber [Oshida Y. Unpublished data, 2012]. This novel process fully utilizes a transformation superplasticity phenomenon, during which the transformation front is under a quasi-liquid (amorphous) state, so that the diffusion rate (in this case, nitrogen gas molecule) is accelerated. Ion implantation, diffusion hardening, and coating are surface modification techniques for improving the wear resistance and surface hardness of Ti alloy surfaces [236–240]. A Ti–6Al–4V sample was diffusion-hardened in a nitrogen atmosphere for 8 h at 566°C and argon- or nitrogen-quenched to room temperature. The nitrogen-diffusion-hardened Ti–6Al–4V alloy had TiN and TiNO complexes at the immediate surface and sub-surface layers. The diffusion-hardened samples also had a deeper penetration of oxygen compared to regular Ti–6Al–4V samples [241].

Surface topography and chemistry have been shown to be extremely important in determining cell–substrate interactions and influencing cellular properties such as cell adhesion, cell–cell reactions, and cytoskeletal organization [242]. The cell–substrate interaction of primary hippocampal neurons with thin films of TiN was studied *in vitro*. TiN films of different surface chemistries and topographies were deposited by pulsed DC reactive magnetron sputtering and closed field unbalanced magnetron sputter ion plating to result in TiN thin films with similar surface chemistries but different topographical features. It was reported that (i) primary hippocampal neurons were found to attach and spread to all of the TiN films, (ii) neuronal network morphology appeared to be more preferential on the nitrogen-rich TiN films, and also reduced nanotopographical features, (iii) at early time points of 1 and 4 days *in vitro* primary hippocampal neurons respond to the presence of interstitial nitrogen rather than differences in nanotopography; however (iv) at 7 days, more preferential neuronal network morphology is formed on TiN thin films with lower roughness values and decreased size of topographical features [242]. Bull and Chalker [243] studied the use of thin titanium interlayers to

promote the adhesion of TiN coatings on a range of substrates. For thin interlayers, an interstitially hardened titanium layer is formed at the interface, resisting the interfacial crack propagation. However, at a critical interlayer thickness, the surface contaminants are completely dissolved in the interfacial layer, and depositing any further titanium leads to an overall softer interfacial layer which offers less resistance to crack propagation, and delamination can easily take place. For this reason, failure is observed within the interlayer for thick interlayers, whereas it occurs at the interlayer/substrate interface for thinner interlayers. Another contribution to the enhanced adhesion comes from the reduction in coating stresses in the interfacial region due to the presence of a soft compliant layer, which was examined by changing the hardness of the interlayer deposited before coating deposition. It was concluded that (i) softer interlayers do not lead to improved adhesion performance in most cases, and (ii) it appears that the best adhesion results from a hard interlayer that leads to ductile failure at the coating/substrate interface, rather than the brittle failure observed due to the presence of oxide films [243].

As briefly described earlier, Oshida et al. [229,244] applied a TiN coating onto CpTi substrate prior to porcelain firing to develop a new method to control the excessive oxidation. The bonding strength of porcelain to metals depends on the oxide layer between the porcelain and the metal substrate. Oxidation of a metal surface increases the bonding strength, whereas excessive oxidation decreases it. Titanium suffers from its violent reactivity with oxygen at high temperatures that yield an excessively thick layer of TiO_2 , and this presents difficulties with porcelain bonding. The oxidation kinetics of titanium simulated to porcelain firing was investigated, and the surface nitridation of CpTi as a process of controlling the oxidation behavior was evaluated. Nitrided samples with the arc ion plating PVD process and unnitrided control CpTi were subjected to oxidation simulating of Procera porcelain with 550°C, 700°C, and 800°C firing temperatures for 10 min in both 1 and 0.1 atmospheric air. The weight difference before and after oxidation was calculated, and the parabolic rate constant, K_p ($\text{mg}^2/\text{cm}^4/\text{s}$), was plotted against inverse absolute temperature (i.e., in an Arrhenius plot). Surface layers of the samples were subjected to X-ray and electron diffraction techniques for phase identifications. Results revealed that both nitrided and unnitrided samples obey a parabolic rate law with activation energy of 50 kcal/mol. In addition, the study shows that nitrided CpTi had a K_p about five times lower than the unnitrided CpTi, and hence the former needs 2.24 times longer oxidation time to show the same degree of oxidation. Phase identification resulted in confirming the presence of TiO_2 as the oxide film in both groups but with 1–2 μm thickness for the unnitrided CpTi and 0.3–0.5 μm thickness for nitrided samples. Therefore, it can be concluded that nitridation of titanium surfaces can be effective in controlling the surface oxide thickness that might ensure satisfactory bonding with porcelain [229]. Oshida et al. [244] evaluated CpTi substrates subjected to porcelain firing and bond strengths under three-point bending mode (span length: 15 mm; crosshead speed: 0.5 mm/min). Experimental variables included surface treatments of CpTi and porcelain firing schedules. Variables for the surface treatments were (1) sandblasting, (2) mono- and triple-layered nitridation, and (3) monolayered

chrome-doped nitridation. Variables for the porcelain firing schedule included (4) bonding agent application, (5) bonding agent plus gold bonding agent application, and (6) Procera porcelain application. Statistically, all of them exhibited no significant differences. Hence, we employed two further criteria: (i) the minimum bond strength should exceed the maximum porcelain strength *per se* and (ii) the CpTi substrate should not be heated close to the β -transus temperature. After applying these criteria, it was concluded that monolayered nitridation and monolayered application of chrome-doped nitridation on both (with and without) sandblasted and nonsandblasted surfaces were the most promising conditions for a successful titanium-porcelain system [244]. It seems that an alloy which has the properties of titanium and is relatively inexpensive would be a very good material for surgical purposes. These requirements could be met, for example, by stainless steel coated with a firmly adhering nonporous titanium film. Gluszek et al. [245] coated 316L (18Cr–8Ni–2Mo with low carbon content) stainless steel with Ti or TiN by ion plating. The galvanic effects for the galvanic couples 316L/Ti, 316L/Ti-coated 316L, 316L/TiN-coated 316L were studied in Ringer's solution. It was concluded that (i) both Ti and TiN coatings were nonporous, (ii) Ti served as an anode in the couple 316L/Ti, whereas for the other two couples, the coatings were the cathodes; however (iii) the dissolution rate of 316L stainless steel in these couples was smaller than expected owing to a strong polarization of the coatings [245].

The characteristics of various titanium surfaces modified by cold plasma nitriding in terms of adhesion and proliferation of rat osteoblast-like cells were evaluated [246]. Samples of CpTi (grade II) were subjected to three different surface modification processes: polishing, nitriding by DC plasma, and nitriding by cathodic cage discharge. To evaluate the effect of the surface treatment on the cellular response, the adhesion and proliferation of osteoblast-like cells (MC3T3) were quantified. Cellular morphology was observed by SEM. It was found that (i) there was more MC3T3 cell attachment on the rougher surfaces produced by cathodic cage discharge compared with polished samples and (ii) plasma nitriding improves titanium surface roughness and wettability, leading to osteoblast-like cell adhesion [246]. Titanium material has limitations in its clinical performance in dental and orthopedic applications. A coating process using PLD technology was investigated to produce surfaces of titanium carbide (TiC) on titanium substrates, and the biological response evaluations both *in vitro* and *in vivo* were performed. XPS analysis revealed the presence of 18.6–21.5% TiC in the surface layer, accompanied by oxides of titanium 78.5–81.4% in the following concentrations: 11.1–13.0% Ti₂O₃, 50.8–55.8% TiO₂, and 14.5–14.7% TiO. It was found that (i) expression of genes central to osteoblast differentiation (ALP, A2 procollagen type 1, OC, BMP4, transforming growth factor- β (TGF- β), and Cbfa-1) were upregulated in all cell lines (primary human osteoblasts, hFOB1.19 and ROS.MER#14) grown on TiC compared with uncoated titanium when measured by semiquantitative PCR and real-time PCR, (ii) whilst genes involved in modulation of osteoclastogenesis and osteoclast activity (IL-6 and M-CSF) were unchanged, (iii) bone density was shown to be greater around TiC-coated implants after 2 and 4 weeks in sheep and both 4 and 8 weeks in rabbits compared to uncoated titanium, and (iv) rapid bone

deposition was demonstrated after only 2 weeks in the rabbit model when visualized with intravital staining. It was concluded that coating with TiC will, in comparison to uncoated titanium, improve implant hardness, biocompatibility through surface stability, and osseointegration through improved bone growth [247].

A carbide layer was formed on the surface of Ti by heating in hydrocarbon atmosphere (benzene C_6H_6) at 1000–1400°C using a high frequency induction heating method. Physical and mechanical properties of carbide-coated Ti were investigated to examine its potential as an abrasion-resistant implant material. SEM showed that the surface of Ti was covered with fine grains of 1–4 μm diameter, depending on heating conditions. In addition, a carbide layer of about 1–25 μm thickness was observed on the cross section of specimens by SEM and EDS. Vickers hardness of surface carbide was found to be more than 2000. Further, Martens scratch tests and ultrasonic scaler abrasion tests showed that the indentation depth and width of carbide-coated Ti were much smaller than pure Ti, thereby confirming its high abrasion resistance. From these results, it was suggested that for Ti implant materials that require high abrasion resistance, such as the abutment for dental implants, surface carbide coatings would be an effective means to improve their wear properties [248].

11.4.6 Ti Coating

Lee et al. [249] conducted the *in vivo* study to evaluate the behavior and mechanical stability in implants of three surface designs, which were smooth surface Ti, rough Ti surface by plasma spray coating, and alkali and heat treated. The implants were inserted transversely in a dog thigh bone and evaluated at 4 weeks of healing. At 4 weeks of healing after implantation in bone, it was found that (i) the healing tissue was more extensively integrated with an alkali- and heat-treated Ti implant than with the implants of smooth surface and/or rough titanium surfaces, (ii) the bone bonding strength (pullout force) between living bone and implant was observed by a universal testing machine, (iii) the pullout forces of the smooth surface Ti, plasma spray-coated Ti, and alkali- and heat-treated Ti implants were 235, 710, and 823 N, respectively, and (iv) histological and mechanical data demonstrated that appropriate surface design selection can improve early bone growth and induce an acceleration of the healing response, thereby improving the potential for implant osseointegration. In order to improve the biocompatibility of functional titanium-based alloys, Sonoda et al. [250] investigated pure titanium coatings on the TiNi shape memory alloy and Ti–6Al–4V alloy by sputtering. A higher-quality thin film and higher growth rate were obtained by the sputtering with a DC source than with an RF source. After the cleaning method was established, the effect of sputtering on the thickness of the film was investigated with DC sputtering. It was concluded that the growth rate of sputtered titanium film was proportional to the applied electric power, and the orientation of the film highly depended on the heating temperature of the substrate [250]. Sonoda et al. [251] further applied this technique to the complete denture base of the Ti–6Al–4V alloy fabricated by superplastic forming. The base was attached to the substrate holder and

cooled by water or heated at 417°C. It was reported that the film deposited on the heated base was superior to that on the cooled one in smoothness, glossiness, uniformity, and covering of the fine cracks [251]. Until the late 1970s, poly(methyl methacrylate) (PMMA) bone cement was the predominant means of fixing a joint replacement implant to the skeletal system. At that time, however, bone cement was implicated as a major contributor to implant loosening because of its brittle nature and poor interfacial relationship with the metallic implant and bone tissue [252–254]. The use of porous coated implants for long-term biological fixation has been receiving an enthusiastic response, especially when the patients are younger and more active [255,256]. The application of Ti plasma-sprayed coatings to Ti–6Al–4V orthopedic implants results in a dramatic decrease in high-cycle fatigue performance. It was noted that the better bonding of the plasma sprayed and heat-treated implants results in a lower high-cycle fatigue strength. As with conventional sintered porous coatings, the application of a coating that contains defects serves as the crack initiator of the high cycle fatigue. It was also mentioned that the addition of the postcoating heat treatment to improve coating bonding strength resulted in a further reduction in the high cycle fatigue strength, most likely due to a higher frequency of bonding sites between the coating and substrate and a more intimate metallurgical bond at those sites [252].

Reclaru et al. [257] investigated the corrosion behavior of Co–Cr–Mo implants with rough Ti coatings, applied by different suppliers by either sintering or vacuum plasma-spraying, and compared the results with those obtained from uncoated material. The OCP, corrosion current, and polarization resistance were determined by electrochemical methods in artificial bone fluid. The Co, Cr, and Ti ions released from the samples into the electrolyte during the polarization extraction technique were analyzed using ICP-MS. It was found that (i) among the Ti-coated samples, the one with the sintered overcoat turned out to be the most resistant, (ii) yet, on an absolute scale, they all showed a corrosion resistance inferior to that of uncoated Co–Cr–Mo or wrought Ti [257]. The degree of the degradation of the implant surface depends on the particular surface treatment employed [23,166,258–260]. Anodization is a common surface treatment for Ti implants. More recently, there has been a growing interest in Ti plasma-sprayed overcoats as a viable alternative to sintered bead or diffusion-bonded fiber metal surfaces, since the inherent roughness of such coatings is believed to favor the osteointegration of the bone [261,262]. Surface treatment plays an important role in the corrosion resistance of Ti. The cement, in spite of having reduced electrical conductivity in comparison to metal, is an ionic transporter, and therefore capable of participating in the corrosion process. The crevice corrosion at the metal–cement interface was studied by Reclaru et al. [263], who reported that in the case of plasma spray surfaces, a process of diffusion of Ti particles in the electrolyte could accompany the crevice corrosion.

Xue et al. [264] modified plasma-sprayed titanium coatings by an alkali treatment. The changes in chemical composition and structure of the coatings were examined by SEM and AES. The results indicated that (i) a net-like microscopic texture feature, which was full of the interconnected fine porosity, appeared on the

surface of alkali-modified titanium coatings, (ii) the surface chemical composition was also altered by alkali modification, and (iii) a sodium titanate compound was formed on the surface of the titanium coating and replaced the native passivating oxide layer. The bone bonding ability of titanium coatings was investigated using a canine model. The histological examination and SEM observation demonstrated that more new bone was formed on the surface of alkali-modified implants and grew more rapidly into the porosity. It was therefore concluded that (i) the alkali-modified implants appose directly to the surrounding bone, (ii) in contrast, a gap was observed at the interface between the as-sprayed implants and bone, (iii) the push-out test showed that alkali-modified implants had higher shear strength than as-sprayed implants after 1 month of implantation, and (iv) an interfacial layer, containing Ti, Ca, and P, was found to form at the interface between the bone and the alkali-modified implant [264].

Borsari et al. [265] developed a new implant surface with the purpose of avoiding as much stress shielding as possible and thus prolong the prosthesis lifespan, and investigated the *in vitro* effect of this new ultra-high roughness and dense Ti (R_a : 74 μm) in comparison with medium (R_a : 18 μm) and high (R_a : 40 μm) roughness and open porous coatings, which were obtained by vacuum plasma-spraying. MG63 osteoblast-like cells were seeded on the tested materials and polystyrene, as control, for 3 and 7 days. It was reported that (i) alkaline phosphatase activity had lower values for high roughness surfaces than medium and ultra-high rough surfaces, (ii) procollagen-I synthesis reduced with increasing roughness, and the lowest data was found for the ultra-high rough surface, (iii) all tested materials showed significantly higher interleukin-6 levels than those of polystyrene at both experimental times, and (iv) the new ultra-high roughness and dense coating provided a good biological response, even though, at least *in vitro*, it behaved similarly to the coatings already used in orthopedics [265]. The bone response to different TPS implants was evaluated in the trabecular femoral condyles of 10 goats by Vercaigne et al. [266]. These implants were provided with three different TPS coatings with an R_a of 16.5, 21.4, and 37.9 μm , respectively. An Al_2O_3 grit-blasted implant with an R_a of 4.7 μm was used as a control. After an implantation period of 3 months, the implants were evaluated histologically and histomorphometrically. Only one implant was not recovered after the evaluation period. It was reported that (i) most of the implants showed a different degree of fibrous tissue alternating with direct bone contact, (ii) complete fibrous encapsulation of the implant was observed in some of the sections, and no signs of delamination of the plasma-sprayed coating was visible, (iii) no significant differences in bone contact were measured between the different types of implants, (iv) histomorphometrical analysis revealed significantly higher bone mass close to the implants (0–500 μm) for treated implants placed in medial femoral condyle and implants placed in the lateral condyle, and (v) at a distance of 500–1500 μm no difference in bone mass measurements between the different implants was observed [266]. Ong et al. [267] *in vivo* evaluated the bone interfacial strength and bone contact length at the plasma sprayed HA and Ti plasma sprayed implants. Noncoated Ti implants were used for control. Cylindrical coated or noncoated implants were implanted in the

dogs' mandibles. Loading of the implants was performed at 12 weeks after implantation. At 12 weeks after implantation (prior to loading) and 1 year after loading, implants were evaluated for interfacial bone–implant strength and bone–implant contact length. It was found that (i) no significant differences in interfacial bone–implant strength for all groups at 12 weeks after implantation and after 1 year loading in normal bone were found; however (ii) bone contact length for HA implants was significantly higher than the Ti plasma sprayed and Ti implants for both periods tested, and (iii) Ti plasma sprayed implants exhibited similar pullout strength compared to the HA implants [267].

Histologically, Ti has been demonstrated to be a highly biocompatible material on account of its good resistance to corrosion, absence of toxic effects on macrophages and fibroblasts, and lack of inflammatory response in peri-implant tissues [268–271]. Ti endosseous dental screws with different surfaces (smooth Ti, Ti plasma-sprayed, alumina oxide SBA, and zirconia SBA) were implanted in femurs and tibiae of sheep for 14 days to investigate the biological evolution of the peri-implant tissues and detachment of Ti debris from the implant surfaces in early healing. Implants were not loaded. It was reported that (i) all samples showed new bone trabeculae and vascularized medullary spaces in those areas where gaps between the implants and host bone were visible, (ii) in contrast, no osteogenesis was induced in the areas where the implants were initially positioned in close contact with the host bone, (iii) the threads of some screws appeared to be deformed where the host bone showed fractures, and (iv) Ti granules of 3–60 μm were detectable only in the peri-implant tissues of Ti plasma–sprayed implants both immediately after surgery and after 14 days, thus suggesting that this phenomenon may be related to the friction of the Ti plasma spray coating during surgical insertion [272].

The biocompatibility of Co–Cr alloy was significantly improved by forming a rough TiO_2 layer on its surface. The TiO_2 layer was formed by coating the Co–Cr alloy with titanium (Ti) through electron beam deposition followed by MAO. When Ti was coated on the surface, the biocompatibility of the Co–Cr alloy was enhanced and it was further improved by the MAO treatment. There were close relationships among the phase, morphology, and thickness of the TiO_2 layer and the applied voltage. The biocompatibility of the specimens coated with Ti and subjected to MAO treatment was evaluated by *in vitro* ALP activity tests [273].

Porous metals (sintered beads and meshes) have been used for many years for different orthopedic applications. Metal foams have been recently developed. These foams have the advantage of being more porous than the traditional coatings. Their high porosity provides more space for bone ingrowth and mechanical interlocking and presents more surface area for implant–bone contact. The objective of this study was to evaluate *in vivo* bone ingrowth into Ti implants covered with a novel Ti foam coating. This foam contains 50% in volume of interconnected pores and a higher surface area compared to dense Ti. Both coated implants and dense Ti controls were placed transcortically in the rat tibiae. The animals were sacrificed at 2 weeks after implantation, and the amount of bone in the implants was determined using backscattered electron imaging and X-ray microtomography. It was found that the pores within the

Ti foam showed 97.7% bone filling, and the bone–implant contact area was significantly increased compared to dense Ti controls, indicating that this novel Ti foam is biocompatible, has the capacity to sustain bone formation, and can potentially improve osteointegration [274].

11.4.7 TiO_2 Film and Coating

The high corrosion resistance and good biocompatibility of Ti and its alloys are due to a thin passive film that consists essentially of TiO_2 . There is increasing evidence, however, that under certain conditions, extensive Ti release may occur *in vivo*. An ion-beam–assisted sputtering deposition technique has been used to deposit thick and dense TiO_2 films on Ti and stainless steel surfaces. A higher electrical film resistance, lower passive current density, and lower donor density (in order of 10^{15} cm^{-3}) have been measured for sputter-deposited oxide film on Ti in contrast to the naturally formed passive oxide film on Ti (donor density in the order of 10^{20} cm^{-3}). It was found that (i) the coated surface exhibited improved corrosion resistance in PBS and (ii) the improved corrosion protection of the sputter-deposited oxide film can be explained by a low defect concentration and, consequently, by a slow mass transport process across the film [275]. The National Industrial Research Institute of Nagoya has established technology for forming a functional gradient Ti–O film on Ti–6Al–4V by the reactive DC sputtering vapor deposition method. The overall film thickness in the experiment was $3 \mu\text{m}$, and the Vickers hardness of the surface was 1500 (vs. CpTi: 200–300) [276].

The conditions for obtaining titanium dioxide from the substrates titanium tetrachloride and oxygen, and applying this to a surgical 316L stainless steel by PACVD were determined. It was established that during the process, Ti dioxide anatase is created. During exposure of the 316L stainless steel with the Ti dioxide coating, in Ringer's solution, it was found that (i) protective properties of this coating improved, (ii) Ti dioxide covering increased the resistivity of 316L stainless steel to pitting corrosion and general corrosion, and (iii) any damage or partial removal of the coating did not cause an increased galvanic corrosion of the substrate [277].

Wollastonite (CaSiO_3) ceramic was studied as a medical material for artificial bones and dental roots because of its good bioactivity and biocompatibility [278,279]. Lui and Ding [280] prepared wollastonite/ TiO_2 composite coating using plasma-spraying technology onto Ti–6Al–4V substrate. The composite coating revealed a lamellar structure with alternating wollastonite coatings and TiO_2 coating. In the case of composite coatings, the primarily crystalline phases of the coatings were wollastonite and rutile, indicating wollastonite and TiO_2 did not react during the plasma-spraying process. It was found that (i) the mean Vickers microhardness of the coatings increased with an increase in the content of TiO_2 . Wollastonite/ TiO_2 composite coatings were soaked in SBF to examine their bioactivity, (ii) a carbonate-containing HA layer was formed on the surface of the wollastonite and composite coatings (wollastonite/ TiO_2 : 7/3) soaked in SBF, while a carbonate-containing HA layer was not formed on the surface of the TiO_2 and

composite (with wollastonite/TiO₂: 3/7) coatings after immersion, and (iii) a silica-rich layer appeared at the interface of the carbonate-containing HA and wollastonite and composite (7/3 with wollastonite/TiO₂) coatings. The cytocompatibility study of osteoblasts seeded onto the surface indicated that the addition of wollastonite promoted the proliferation of osteoblasts [280].

Fraichinger et al. [281] utilized the anodic plasma-chemical (APC) process to modify CpTi surfaces. This technique allowed for the combined chemical and morphological modifications of Ti surfaces in a single step. The resulting conversion coating, typically several micrometers thick, consisted mainly of Ti oxide and significant amounts of electrolyte constituents. A new electrolyte was developed containing both calcium-stabilized by complexation with EDTA (as a chelating agent) and phosphate ions at pH 14. The presence of the Ca–EDTA complex, negatively charged at high pH, favors incorporation of high amounts of Ca into the APC coatings during the anodic (positive) polarization. It was reported that (i) the maximum Ca/P atomic ratio in the coating produced with the new APC electrolyte was approximately 1.3, with higher Ca concentrations than reported in conventional APC coatings, (ii) the coating produced in the new electrolyte system exhibited favorable mechanical stability, and (iii) the new APC technology is believed to be a versatile coating technique to render titanium implant surfaces bioactive [281].

Haddow et al. [282] investigated the effects of dip rate, sintering temperatures, and time on the chemical composition of the titania films, their physical structure and thickness, and adherence to a silica substrate. In order to produce films, the sol–gel method was employed. By this method, films can be made to mimic as closely as possible the natural oxide layer that is found on titanium. CpTi (grade IV) isopropoxide was dissolved in isopropanol to form the starting sol. Due to the ease of hydrolysis of this sol, a chelating agent, diethanolamine, was added. A small amount of water was added to the sol of alkoxide to partially polymerize the Ti species. Thin surface films of titania have been deposited onto glass substrates. These films are to be used as substrates in an *in vitro* model of osseointegration. If titania has been deposited onto glass substrates, the use of low dipping rates prevents cracking in the films, irrespective of the subsequent firing time or temperature. Firing at higher temperature (600°C) produces predominantly glass films and mimic closely, in chemistry, the natural oxide layer that is formed on Ti implants. Refinement of the dipping setup, or the use of dilute solutions, may result in the production of thinner films. Thinner films will almost certainly be crack-free after firing, and may result in fewer organic products being trapped in the film during the firing process. It was mentioned that (i) these data are important when using the titania films to develop an *in vitro* model to study the phenomenon of osseointegration and (ii) coatings may be deposited onto a wide range of materials; this would be particularly beneficial, enabling the study of osseointegration by TEM and photon-based spectroscopies [282]. Sato et al. [283] used the sol–gel processing to coat Ti substrates with HA, TiO₂, and poly(DL-lactic-glycolic acid). Coatings were evaluated by cytocompatibility testing with osteoblast-like cells (or bone-forming cells). The cytocompatibility of the HA composite coatings was compared to that of a traditional PSHA coating. Results showed that (i) osteoblast-like

cell adhesion was promoted on the novel HA sol–gel coating compared to the traditional PSHA coating and (ii) hydrothermal treatment of the sol–gel coating improved osteoblast-like cell adhesion [283]. Wang et al. [284] treated an amorphous titania gel layer on the CpTi surface after the Ti surface was treated with a $\text{H}_2\text{O}_2/\text{HCl}$ solution at 80°C . The thickness of the gel layer increased almost linearly with the period of the treatment. It was found that (i) a subsequent heat treatment above 300°C transformed gradually the amorphous gels to the anatase crystal structure, and the rutile started to appear after heat treatment at 600°C , and (ii) similar to the sol–gel-derived titania gel coatings, titania gel layers exhibited *in vitro* AP deposition ability after the gel layers exceeded a minimum thickness ($0.2\text{ }\mu\text{m}$) and was subsequently heated in a proper temperature range ($400\text{--}600^\circ\text{C}$) [284].

Titania (5–20 mol%) was mixed with pure HA or HA containing Ag_2O (10–20 mol%) and was heated at 900°C for 12 h. The sintered samples were found to contain mainly TCP (β -TCP). Enhanced TCP formation with impurity was observed with $\text{TiO}_2\text{--Ag}_2\text{O}$ addition. An *in vitro* solubility study in phosphate buffer at physiological conditions showed the resorbable nature of these materials. It was also mentioned that the gradually functional material structure was formed by spreading a $\text{TiO}_2\text{--Ag}_2\text{O}$ mixture on the surface of the HA green compact and heating at 900°C [285].

AP is known to show excellent absorbability of bacteria, ammonia, nitrogen oxides, or aldehyde—environment-purification material. One major drawback of AP is that absorbed materials will sooner or later be saturated on AP surfaces. At the same time, as was briefly discussed in Chapter 4, it is known that TiO_2 is a photocatalyst. A photocatalyst is a material that absorbs light to bring it to a higher energy level and provides such energy to reacting substances to enable chemical reaction to take place. When the photocatalyst absorbs the light, positive holes are created in the valence electron band to react with electrons. A positive hole of TiO_2 reacts with water or dissolved oxygen to generate OH radicals, which decompose toxic substances. The OH radicals possess stronger oxidation power than chlorine or ozone for sterilization or disinfection. Hence, a multiple functional ceramic composite can be fabricated to achieve those specific aims. TiO_2 particles or a base substrate layer can be partially coated with AP to make their respective materials function individually: specifically, AP absorbs bacteria or organic materials and TiO_2 can decompose such toxic materials. Since absorbed species on AP are decomposed by the TiO_2 catalyst, the original absorbability of AP can always be maintained [286,287].

The biocompatibility of titanium surfaces was evaluated by modifying surfaces in two different ways: (i) deposition of a bioinert, thin film of rutile TiO_2 by chemical vapor deposition (MOCVD) and (ii) biochemical treatment with collagen gel, in order to obtain a biointeractive coating. Behind the comparison is the idea that either the bioinert or the bioactive coating has specific advantages when applied to implant treatment, such as the low price of the collagen treatment, for instance. The stability in buffer solution was evaluated by OCP for medium time and cyclic voltammetry. The OCP stabilized after $5 \times 10^4\text{ min}$ for all the specimens except the collagen-treated sample which presented a stable OCP from the first minutes.

MOCVD-treated samples stabilized to more electropositive values. Human dermal fibroblasts were selected for cell culture tests, taking into account that these cells are present in all biointerfaces, being the main cellular type of connective tissue. The cells grew on either type of surface without phenotype modification. Cell spreading, as evaluated from microscope images processed by the program Sigma Scan, also showed enhancement upon surface modification. It was found that, depending on the experimental conditions, MOCVD-deposited TiO_2 exhibits different nanostructures that may influence biological behavior, demonstrating the capacity for integration in simulated physiologic liquids for an implant pretreated by either method [288]. Nanocrystalline titanium dioxide particles and films with anatase structures have been prepared via the solvothermal method under low temperature. The products were characterized by XRD and TEM, SEM, and AFM. The optical properties were characterized in the UV/VIS region by optical absorption measurement. The relationship between the optical band gaps and the structures was studied [289]. The crystal structure and surface morphology of anodic films on titanium metal were studied in different electrolytes under various electrochemical conditions and the effect of the crystal structure of the oxide films on AP-forming ability in SBF was investigated. Titanium oxide films were prepared using an anodic oxidation method on the surface of titanium metal in four different electrolytes: sulfuric acid, acetic acid, phosphoric acid, and sodium sulfate solutions with different voltages for 1 min at room temperature. It was reported that (i) anodic films that consisted of rutile and/or anatase phases with porous structures were formed on titanium metal after anodizing in H_2SO_4 and Na_2SO_4 electrolytes, while amorphous titania films were produced after anodizing in CH_3COOH and H_3PO_4 electrolytes and (ii) titanium metal with the anatase and/or rutile crystal structure films showed excellent AP-forming ability and produced a compact AP layer covering all the surface of titanium after soaking in SBF for 7 days, but titanium metal with amorphous titania layers was not able to induce AP formation. It was therefore concluded that the resultant AP layer formed on titanium metal in SBF could enhance the bonding strength between living tissue and the implant and anodic oxidation is believed to be an effective method for preparing bioactive titanium metal as an artificial bone substitute even under load-bearing conditions [290].

Nanostructured materials may play a significant role in controlled release of pharmacologic agents for treatment of cancer. Many nanoporous polymer materials are inadequate for use in drug delivery. Nanoporous alumina provides several advantages over other materials for use in controlled drug delivery and other medical applications. Atomic layer deposition was used to coat all the surfaces of a nanoporous alumina membrane in order to reduce the pore size in a controlled manner. Neither the 20 nm nor the 100 nm TiO_2 -coated nanoporous alumina membranes exhibited statistically lower viability compared to the uncoated nanoporous alumina membrane control materials. Nanostructured materials prepared using atomic layer deposition may be useful for delivering a pharmacologic agent at a precise rate to a specific location in the body. These materials may serve as the basis for “smart” drug delivery devices, orthopedic implants, or self-sterilizing medical devices [291]. Silicon-incorporated TiO_2 coating (Si-TiO_2) was prepared

on titanium (Ti) by MAO technique in the Ca-, P-, Si-containing electrolyte. The surface topography, phase, and element composition of the coatings were characterized by SEM, XRD, and EDS, respectively. Osteoblast-like MC3T3-E1 cells were cultured on the surface of the coatings to evaluate their adhesion behavior. The obtained results showed that Si element was successfully incorporated into the porous TiO₂ coating, which did not apparently alter the surface topography and phase composition of the coating. The adhesion of the MC3T3-E1 cells on the Si-incorporated TiO₂ coating was significantly enhanced compared with the Si-free TiO₂ coating and pure Ti plates. In addition, the enhanced cell adhesion may at least partly be mediated by an integrin β 1-FAK signal transduction pathway. It was suggested that the Si-TiO₂ coating is worth further consideration for orthopedic implant applications [292].

A series of sol-gel-derived TiO₂-SiO₂ mixed oxide coatings were prepared by carefully controlling the process parameters to obtain silica-releasing coatings consisting of nanoparticles. These features are of paramount importance for enhanced cell adhesion and activation. To achieve both these goals the Ti-alkoxide and Si-alkoxide were first separately hydrolyzed and the titania-silica mixed sol was further reacted before the dipping process to obtain the desired particle sizes resulting to the biologically favorable topographical features. Silica release was observed from all the prepared coatings and it was dependent on SiO₂ amount added to the sols, that is, the higher the added amount the higher the release. In addition, calcium phosphate was able to nucleate on the coatings. From the obtained SiO₂ dissolution data, together with the detailed XPS peak analysis, the mixed oxide coatings are concluded to be chemically heterogeneous, consisting of TiO₂ and SiO₂ species most likely linked together by Ti-O-Si bonds. TiO₂ is chemically stable, making long-term implant coating possible, and the desired nanoscale dimensions were well preserved although the composition was changed as a consequence of SiO₂ dissolution under *in vitro* conditions [293].

Zinc element was incorporated into TiO₂ coatings on titanium by plasma electrolytic oxidation to obtain the implant with good bacterial inhibition ability and bone formability [294]. The porous and nanostructured Zn-incorporated TiO₂ coatings are built up from pores smaller than 5 μ m and grains 20–100 nm in size, in which the element Zn exists as ZnO. The results obtained from the antibacterial studies suggest that the Zn-incorporated TiO₂ coatings can greatly inhibit the growth of both *Staphylococcus aureus* and *Escherichia coli*, and the ability to inhibit bacteria can be improved by increasing the Zn content in the coatings. Moreover, the *in vitro* cytocompatibility evaluation demonstrates that the adhesion, proliferation, and differentiation of rat bMSCs on Zn-incorporated coatings are significantly enhanced compared with Zn-free coating and CpTi plate, and no cytotoxicity appeared on any of the Zn-incorporated TiO₂ coatings. Moreover, bMSC express higher level of ALP activity on Zn-incorporated TiO₂ coatings and are induced to differentiate into osteoblast cells. The better antibacterial activity, cytocompatibility, and the capability to promote bMSC osteogenic differentiation of Zn-incorporated TiO₂ coatings may be attributed to the fact that Zn ions can be slowly and constantly released from the coatings. Based on the aforementioned

results, it was concluded that innovative Zn-incorporated TiO_2 coatings on titanium with excellent antibacterial activity and biocompatibility are promising candidates for orthopedic and dental implants [294].

Although titanium has been successful as an orthopedic or dental implant material, performance problems still persist concerning implant–bone interfacial bonding strength. A novel oxygen-diffused titanium (ODTi), fabricated by introducing oxygen into the titanium crystal lattice by thermal treatment, was investigated. The fabricated material is the result of a surface modification made on CpTi previously coated with poly(vinyl alcohol) by means of a thermal treatment performed at 700°C in an ultra-pure argon atmosphere. The thermal treatment at 700°C led to the formation of an anatase TiO_2 film on the CpTi surface and a concentration gradient of oxygen into titanium. The surface of the fabricated ODTi consisted of an outer nanometric layer of anatase TiO_2 and an inner nanometric layer of Ti_2O_x ($x < 1$) in which the oxygen is in solid solution with the titanium metal. It was found that ODTi possesses *in vitro* AP formation ability after being soaked into SBF solution. It was also mentioned that the AP formation ability is attributed to the presence of the anatase TiO_2 outermost surface layer and to abundant hydroxyl groups ($-\text{OH}$) formed on the ODTi surface after immersion in SBF [295].

11.4.8 Other Coatings

Tanaka et al. [296] investigated the interfacial microstructure between gold-coated titanium and low-fusing porcelain. The square surfaces of cast titanium split rods were sputter-coated with gold using a sputter coater at 40 mA for 1000 s. Specimens were prepared for TEM by cutting and polishing two pieces of the gold-coated split-rod specimens, which were glued and embedded in Cu tubes with an epoxy adhesive. TEM observation was also conducted for the gold-coated specimens after degassing and porcelain fusing. Due to the gold coating, intermetallic compounds of Au–Ti formed under the sputtered gold layer after degassing and porcelain fusing. Ti_3Au and Ti_3Al layers were also observed beneath the Au–Ti intermetallic compound layer. It was observed that there was good adhesion of porcelain to the Au–Ti compound and Ti oxides without any gaps or formation of a Ti-deficient intermediate layer, which is normally observed at the titanium–porcelain interface. It was further suggested that gold-sputter-coating the cast titanium surface produced a Ti–Au intermetallic compound and suppressed the formation of a Ti-deficient intermediate layer, resulting in improved adherence between porcelain and titanium [296].

Selenium (Se) nanoclusters were grown through heterogeneous nucleation on titanium (Ti) surfaces. Normal healthy osteoblasts (bone-forming cells) and cancerous osteoblasts (osteosarcoma) were cultured on the Se-doped surfaces having three different coating densities. For the first time, it is shown that substrates with Se nanoclusters promote normal osteoblast proliferation and inhibit cancerous osteoblast growth in both separate (monoculture) and coculture experiment. It was suggested that Se surface nanoclusters can be properly engineered to inhibit bone

cancer growth while simultaneously promoting the growth of normal bone tissue [297].

Functionally graded, hard, and wear-resistant Co–Cr–Mo alloy was coated on Ti–6Al–4V alloy with a metallurgically sound interface using Laser Engineering Net Shaping (LENS™). The addition of the Co–Cr–Mo alloy onto the surface of Ti–6Al–4V alloy significantly increased the surface hardness without any inter-metallic phases in the transition region. A 100% Co–Cr–Mo transition from Ti–6Al–4V was difficult to produce due to cracking. However, using optimized LENS™ processing parameters, crack-free coatings containing up to 86% Co–Cr–Mo were deposited on Ti–6Al–4V alloy with excellent reproducibility. Human osteoblast cells were cultured to test *in vitro* biocompatibility of the coatings. Based on *in vitro* biocompatibility, increasing the Co–Cr–Mo concentration in the coating reduced the live cell numbers after 14 days of culture on the coating compared with base Ti–6Al–4V alloy. However, coated samples always showed better bone cell proliferation than 100% Co–Cr–Mo alloy. It was mentioned that producing near net shape components with graded compositions using LENS™ could potentially be a viable route for manufacturing unitized structures for metal-on-metal prosthetic devices to minimize the wear-induced osteolysis and aseptic loosening that are significant problems in current implant design [298].

Suh et al. [299] investigated the effects of a nanostructured calcium coating on the surfaces of blasted Ti implants on peri-implant bone formation in the rabbit tibiae. Threaded implants (3.75 mm in diameter, 6 mm in length) were roughened by HA blasting (control; blasted implants). The implants were then hydrothermally treated in a Ca-containing solution for 24 h to prepare Ca-incorporated Ti surfaces (experimental; blasted/Ca implants). Forty-two implants (21 control and 21 experimental) were placed in the proximal tibiae of seven New Zealand White rabbits. Each rabbit received six implants. To evaluate the effects of the nanostructured Ca coating on the peri-implant bone-healing response, removal torque tests and histomorphometric analyses were performed 6 weeks after surgery. It was found that (i) Ca coating did not significantly change the surface properties produced by blasting at the micron level, (ii) histologically, active bone apposition was observed in the blasted/Ca implants in the marrow space, (iii) compared with the blasted implants, the blasted/Ca implants showed significantly increased BIC over the total implant length and greater mean removal torque values, and (iv) the nanostructured, Ca-incorporated surface significantly enhanced the peri-implant bone-healing response of HA-blasted Ti implants. It was concluded that the use of nanostructured, Ca-coated surfaces may have synergic effects in enhancing osseointegration of blasted Ti implants due to their micron-scaled surface properties and biologically active surface chemistry [299].

Brunot et al. [300] investigated to optimize the tissue–titanium interface by applying polyelectrolyte multilayer films on the surface of titanium. The experimental study was undertaken on pure titanium samples. Two types of film ending with polycations or polyanions were selected. Both film types were built with a first poly(ethyleneimine) (*pei*) base layer and composed either of poly(styrene sulfonate) (*pss*) and poly(allylamine hydrochloride) (*pah*) or of hyaluronic acid (*ha*)

and *pll* layers. Final architectures were as follows: *pei-(pss/pah)₁₀*, or *pei-(pss/pah)₁₀-pss*, or chemically cross-linked *pei-(hal/pll)₁₀* or *pei-(hal/pll)₁₀-ha*. An analysis of the physicochemical characteristics of the surfaces was carried out by tensiometry measurements (dynamic contact angle, wettability, and contact angle hysteresis) and AFM. A biological study with human fibroblasts was followed over a 7-day culture period at days 0, 2, 4, and 7 to observe the cellular response in terms of morphology (SEM) and viability (Mosmann's test). It was reported that (i) polyelectrolyte multilayer films could be successfully deposited onto titanium as previously described for glass or composite, (ii) fibroblast adhesion and proliferation was strongly dependent on film type, (iii) SEM observations of cells on the different films agreed with the viability cell test, and (iv) furthermore, films containing *pss/pah* generated a better cellular response than films containing cross-linked *hal/pll*. Based on these findings, it was concluded that *pss/pah* polyelectrolyte films coating titanium could represent a new approach for oral biointegration with great potential for clinical application in the fields of dental implantology, and more particularly, the specific biofunctionalization of *pss/pah* films coating titanium could be envisioned by introducing layers of molecules that encourage the biointegration process between the films [300].

Laser surface engineering (LSE) is advanced enough to modify the surface. A high-power laser beam melts a ceramic powder precursor along with a thin layer of the substrate to produce a laser melt zone. High cooling rates produce metastable (or noncrystalline) phases by exceeding the solid solubility limit of the equilibrium phase diagram. This leads to the possibility of a wide variety of microstructures having novel properties that cannot be produced by any conventional processing technique. The produced TiB_2 is a transition metal-based refractory ceramic that has the unique properties of high hardness, high melting point, wear resistance, corrosion resistance, electrical conductivity, and MOE of 477 GPa [301].

11.5 Collagen, Protein, and CHI Coating

The high success rates for the dental rehabilitation of patients with endosseous implants have resulted from many research approaches with the aim of enhancing and accelerating bone anchorage to the implant, thereby providing optimal support for the intraoral prosthetic devices. This revolutionary breakthrough first evolved from the research efforts of the Brånemark group in the late 1960s by pioneering the insertion of machined screw-type CpTi implants with minimum surgical trauma and a consolidation period for the healing of the bone. This first endosseous titanium implant was produced with an industrial turning process, which led to surfaces with minimally rough topographies at the micron level. The bone bonding ability of this machined implant was mainly the result of the proper surgical technique providing macrostability to the implant and the biocompatible nature of the bulk titanium. In the past three decades, much has been learned about the concept of osseointegration, and significant improvements on the design and surface of

implants were done to eliminate the important challenges of implant dentistry. Osseointegration was first defined as a direct contact between living bone and the surface of a load-carrying implant at the histological level [302] and, in clinical terms, as a biomechanical phenomenon whereby clinically asymptomatic rigid fixation of the implant is achieved and maintained in bone during functional loading [303–305]. Various studies have also suggested that titanium exhibits a better biocompatible nature and less foreign body reaction compared to other conventional materials [306,307]. It has been stated that osseointegration of titanium does not result due to a positive tissue reaction; instead, it occurs in the absence of a negative tissue response [308,309]. Therefore, the bioinert character of titanium is the main reason for its enhanced bone-bonding behavior. Now, osseointegration of titanium is widely accepted as the prerequisite for dental implant success. Although the reported success rates are higher than 90% in controlled clinical trials [310,311], important challenges, such as the long latency period between implant placement and loading, remain to be elucidated. Also, achieving high success rates in specific patient groups (e.g., diabetics, oncology patients, and smokers) seems to be elusive [312]. Over the past two decades, elevating the local quality and quantity of the host tissue for an optimal osseointegration was the major goal of implant dentistry in order to overcome these drawbacks. Therefore, various approaches have focused on finding alternative methods to accelerate and optimize osseointegration, aiming at sufficient mechanical integrity to withstand occlusal forces at an early period [313].

During the first 10–20 years of understanding the healing mechanisms of traumatized bone where implants are placed, the concept that successful osseointegration was the result of titanium implant biocompatibility dominated clinical thinking. Subsequently, implant surface modifications encouraged new considerations of improvements in bone formation at the implant surface. Since the biological mechanisms at the bone–implant interface determine the fate of the implant, characteristics of the implant surface play a central role in challenging the process of osseointegration with early loading. Upon insertion, premature loading can disrupt the healing process and may result in early failure of the implant. Enhancing the biological response using a surface science approach has therefore attracted the attention of many research groups [314,315]. It is well established that characteristics of the implant surface, such as nano- and microtopography and physicochemical composition, have a major influence on the outcome of osseointegration, especially at the histological level, aiming at biological and morphological compatibilities [316].

In general, the implantation of devices for the maintenance or restoration of a body function imposes extraordinary requirements on the materials of construction. Foremost among these is an issue of biocompatibility. It was found, after extensive literature review, that there are three major required compatibilities for placed implants to exhibit biointegration with the receiving hard tissue and biofunctionality thereafter. They include biological compatibility (also known as biocompatibility), mechanical compatibility, and morphological compatibility with receiving host tissues [317–319]. Accordingly, numerous studies have been conducted to meet

the aforementioned requirements for successful implant systems (i.e., mechanical compatibility, biological compatibility, and morphological compatibility) by altering surface characteristics for overcoming the potential drawbacks of the implant therapy [320,321]. This section focuses on essential mechanisms governing the peri-implant healing and surface science approaches for enhancing osseointegration. The future of implant surface science and prospective tissue engineering attempts for the biological constitution of the peri-implant area are also topics of this section that may provide ideas for forthcoming studies.

If dental implantology is an increasingly successful treatment modality, why should we still need to understand the mechanisms of peri-implant bone healing? Are there differences in cortical and trabecular healing? What does “poor quality” bone mean? What stages of healing are most important? How do calcium phosphate-coated implants accelerate healing? What is the mechanism of bone bonding? While there are still many aspects of peri-implant healing that need to be elucidated, it is now possible to deconvolute this biological reaction cascade, both phenomenologically and experimentally, into three distinct phases that mirror the evolution of bone into an exquisite tissue capable of regeneration. The first and most important healing phase, osteoconduction, relies on the recruitment and migration of osteogenic cells to the implant surface, through the residue of the peri-implant blood clot. Among the most important aspects of osteoconduction are the knock-on effects generated at the implant surface, by the initiation of platelet activation, which result in directed osteogenic cell migration. The second healing phase, *de novo* bone formation, results in a mineralized interfacial matrix equivalent to that seen in the cement line in natural bone tissue. These two healing phases, osteoconduction and *de novo* bone formation, result in contact osteogenesis and, given an appropriate implant surface, bone bonding. The third healing phase, bone remodeling, relies on slower processes and is not considered here. This discussion paper argues that it is the very success of dental implants that is driving their increased use in ever more challenging clinical situations and that many of the most important steps in the peri-implant healing cascade are profoundly influenced by implant surface microtopography. By understanding what is important in peri-implant bone healing, we are now able to answer all the questions listed above [322].

Given the popularity of cementless orthopedic implants, it is imperative for orthopedic surgeons to have a basic understanding of the process of peri-implant bone healing. Contact and distance osteogenesis have been used to explain peri-implant bone healing. In contact osteogenesis, *de novo* bone forms on the implant surface, while in distance osteogenesis, the bone grows from the old bone surface toward the implant surface in an appositional manner. Contact osteogenesis may lead to bone bonding if the surface of the implant displays the appropriate surface topography. The early stage of peri-implant bone healing is very important and involves the body's initial response to a foreign material: protein adsorption, platelet activation, coagulation, and inflammation. This results in the formation of a stable fibrin clot that is a depot for growth factors and allows for osteoconduction. Osteoconduction is the migration and differentiation of osteogenic cells, such as

pericytes, into osteoblasts. Osteoconduction allows for contact osteogenesis to occur at the implant surface. The late stage of healing involves the remodeling of this woven bone. In many respects, this process is similar to the bone healing occurring at a fracture site [323].

Ossification mechanisms that occur following the placement of the implant are very important for understanding the biologic response to endosseous implants. Osborn [324] categorized this bioresponse into the following three groups: (1) biotolerant type, characterized by distance osteogenesis; the implant is not rejected from the tissue, but it is surrounded by a fibrous connective tissue, (2) bioinert type, characterized by contact osteogenesis; the osteogenic cells migrate directly to the surface where they will establish *de novo* bone formation, and (3) bioreactive type; the implant allows new bone formation around itself, thereby exchanging ions to create a chemical bond with the bone. Upon insertion, various implant materials exhibit different biologic responses. While biotolerant materials, such as gold, cobalt–chromium alloys, stainless steel, PE, and PMMA, exhibit distance osteogenesis, titanium and titanium alloys are accepted to be bioinert according to their surface oxides [325]. Besides, the rutile-type oxide, which is formed on titanium as a titanium dioxide, is described as a stable crystalline form similar to ceramics in its bioreactive behavior [326]. Although titanium has superior characteristics compared to other implant metals, the osteoconductivity of titanium is lower than calcium phosphate (Ca-P)–based bioceramics [327]. Therefore, Ca-P-based ceramics are referred to as bone-bonding materials, whereas titanium is a nonbonding material to bone [328]. Therefore, approaches have mainly focused on enhancing the bioactivity of titanium and providing a higher osteoconductivity to the bulk material by altering the surface properties.

The character of the host tissue also plays an important role on the ossification mechanism following implantation. Understanding the different peri-implant healing cascades of the cortical and trabecular bone is crucial for better orientating the osseointegration in poor quality bone [329]. Following surgical trauma, the vascular injury of the cortex results in death of the peri-implant cortical bone and is followed by a slow proceeding osteoclastic remodeling. The removal of the injured tissue by osteoclasts and the subsequent formation of the new bone is a long-lasting process. Therefore, the healing around the implant in cortical bone results in distance osteogenesis. Although this slow remodeling phase provides early stability in cortical bone leading to a low rate of implant failure [330], especially in the parasymphyseal mandible, it is a handicap for the surface science approaches for enhancing the osseointegration histologically. On the other hand, the trabecular bone enables the migration of osteogenic cells due to its marrow component. The colonization of differentiating progenitor cells on the implant surface and *de novo* bone formation provides the evidence that peri-implant healing in trabecular bone occurs via contact osteogenesis. In fact, the presence of osteoprogenitor populations in the spongy bone, which is characterized to be of poor quality in implant dentistry (Lekholm and Zarb type III and IV bone), favors the migration and bone-forming activity of these cells directly on the surface when the implant is considered to be bioinert [331]. In recent decades, the development of novel

osteoconductive titanium surfaces that increased the local quantity and quality of osseous tissue at the interface thereby improved the success of implants, especially in regions of the jaw such as the edentulous posterior maxillae where the cortical thickness is frequently insufficient for the primary stability.

The surgical placement of the implant results in injury of the host bone. If the implant is considered to be bioinert, the body responds to this injury with physiological mechanisms similar to a bone fracture healing. Following implant placement, the implant surface first gets in contact with the blood originating from the injured vessels facing the implant cavity. After several seconds, the surface is completely covered with a thin layer of serum proteins. This protein modification of the surface occurs for all implant materials in the same way. However, the type and surface characteristics of the material have a major influence on the structure and conformation of this protein layer [332]. Shortly after protein adsorption, the surface becomes associated with thrombocytes. As a result of thrombocyte aggregation and degranulation on the surface, coagulation mechanisms take place and cytokines (e.g., TGF- β and platelet-derived growth factor (PDGF)) and several vasoactive factors (e.g., serotonin and histamine) are released from cytoplasmic granules of thrombocytes. These chemoattractants stimulate proliferation and migration of various cells, thereby orientating the peri-implant healing mechanisms [333]. For example, PDGF has important mitogenic and migrative effects on several cell types, such as inflammatory leukocytes, osteoblasts, smooth muscle cells, and fibroblasts [334].

PMNs are also the first group of cells that play an important role in the inflammatory response. PMNs dominate the bone–implant interface on the first and second days. The number of PMNs tends to decrease when bacteria and endotoxins are not present at the interface. At the second day of healing, monocyte migration and macrophage accumulation starts to take place [322]. PMNs and macrophages remove dead cells, ECM residues, and bacteria. Besides their role in the initial inflammatory phase, another mission of macrophages is the expression of cytokines, such as fibroblast growth factor (FGF), PDGF, and vascular endothelial growth factor (VEGF). Thus, they provide important signals to stimulate the recruitment of osteogenic and endothelial progenitors for the next proliferative phase. The release of vasoactive amines, thrombocyte and leukocyte infiltration, the establishment of the coagulum and fibrin network, and macrophage actions are important events that occur at the inflammatory phase. This first phase, which can sometimes extend to 5 days, is followed by the removal of the coagulum by PMNs and subsequently by monocytes; at the same time, angiogenesis also starts to take place [308]. The growth of new capillaries into the fibrin network is mostly stimulated by the growth factors (primarily FGF and VEGF) expressed by macrophages and endothelial cells as a response to the hypoxic and acidic nature of the bone–implant interface [335]. In this way, the proliferation, maturation, and organization of endothelial cells to new capillary tubes take place, thereby providing oxygen and nutrients to the newly formed tissue at the interface.

The behavior of blood cells inside the fibrin-based structural matrix has a major impact on the healing mechanisms at the bone–implant interface. In addition, the

quality of bone healing around an implant is also affected by the capacity of osteogenic cells to proliferate and migrate. Meyer et al. [336] have demonstrated that the osteoprogenitor cells started to attach to the implant surface after 1 day following insertion. This was a similar finding, as stated by Davis [329], showing that early recruitment and colonization of MSCs occur on an implant surface in a short time through modulation of white blood cells, fibrin networks, and thrombocytes [337]. The three-dimensional structure of the fibrin matrix and the migrating effects of growth factors expressed by the first arriving cells play an important role in the establishment of an osteoprogenitor reservoir at the interface. Therefore, the chemistry of the implant material and its surface characteristics are of special interest in implantology, since they initially influence the binding capacity of fibrin and the release of growth factors, thereby directly affecting the migration of mesenchymal cells [338].

Titanium implant materials possess ideal fibrin retention on their surface. Through this fibrin matrix, osteogenic cells having migration ability arrive at the implant surface and start to produce bone directly on the surface. Davies [324] termed this phenomenon *de novo* bone formation through contact osteogenesis. Upon arrival at the surface, the differentiated osteogenic cells secrete the collagen-free matrix (cement lines/lamina limitans) for mineralization through calcium and phosphate precipitation. This layer, where the initial mineralization occurs, consists of noncollagenous proteins (mostly osteopontin and BSP) and proteoglycans [339]. Following calcium phosphate precipitation, the formation and mineralization of collagen fibers take place. Thus, a noncollagenous tissue is established between the implant surface and the calcified collagen compartment through contact osteogenesis. This intermediary tissue is very important for understanding the bonding mechanism between bone and bioinert titanium implant. Following the establishment of the calcified matrix on the implant surface, woven bone formation and organization of the bone trabeculae start to take place for the reconstitution of the damaged bone at the peri-implant area [331]. Since the woven bone consists mostly of irregular-shaped and loosely packed collagen fibers, it does not provide sufficient mechanical stability compared to the organized lamellar bone. However, most woven bone usually remodels in 3 months and is replaced by lamellar bone. At 3 months of healing, the implant is mostly surrounded by a mixture of woven and lamellar bone [340]. The formation and remodeling of the new lamellar bone around the implant occur more rapidly in the regions where there is denser marrow component present. Therefore, the biologic fixation of the implant is achieved faster in the trabecular bone, while a better primary stability is obtained in the cortical bone following implantation.

An implant surface is considered to be clean following fabrication processes. If not stored under special conditions, contaminations (e.g., hydrocarbon, sulfur dioxide, and nitric oxide) occur from the atmosphere [341]. In order to decrease and eliminate such risk of contamination, commercial implant surfaces are usually subjected to passivation treatments and stored carefully in optimal packages until usage. If such an implant is placed into bone, its surface first comes in contact with blood, which is mostly composed of water molecules. Different from liquid water,

the water molecules bind to the surface and form a water mono- or bilayer [342]. The organization of water molecules differs according to the wettability characteristics of the surface [343]. While on hydrophilic surfaces the interaction with water molecules results in the dissociation of molecules and in the formation of hydroxyl groups, the water-binding capacity of hydrophobic surfaces is very low. Following the establishment of a water overlayer, the ions (e.g., Cl^- and Na^+) enter the layer and become hydrated. The characteristics of an implant surface have a major impact on this arrangement of ions and their water shells. After the establishment of an intermediate layer composed of ions and water molecules, the biomolecules arrive at the surface in milliseconds. Proteins adsorb first onto the surface, then change their conformation, denaturize, and desorb from the surface, leaving their place to other proteins that have more affinity to the surface. Thus, a biologic layer with a different arrangement and conformation surrounds the surface.

It is well known that surface characteristics have an important effect on the adsorption of biomolecules by changing the arrangement of water molecules and ions [338]. While on hydrophobic surfaces, proteins bind with their hydrophobic regions and on hydrophilic surfaces the connection is established with the help of hydrophilic regions [342]. This protein overlayer is never considered to be static. It is subjected to structural and conformational changes in time. Normally the protein, which is found in higher concentration in the biological fluid, reaches and adsorbs to the surface first. Usually, this protein is replaced afterwards with another one that has more affinity to the surface, although its concentration is low in the biological fluid. As a result of these adsorption and desorption mechanisms, a diverse layer composed of different protein is formed and maintained at the surface. The major role of this protein layer is the attachment of functionary cells of the healing process. If a bone implant is planning to be developed, the establishment of a surface that generates an optimal protein composition and conformation for the attachment of osteogenic cells on itself is one of the most important strategies of the production.

Several proteins (e.g., fibronectin, vitronectin, laminin, serum albumin, and collagen) facilitate the attachment of osteogenic cells on titanium surfaces [344,345]. Therefore, the protein-binding capacity of an implant surface is considered to be an important factor for successful osseointegration, since surface properties, such as micro- and nanotopography [346], physicochemical composition [344], and surface free energy [59], have an influence on the extend of protein adsorption. It has been documented that osteogenic cells preferably attach to the specific protein sequences, such as the arginine–glycine–aspartic acid (RGD) motif. This motif is found in various ECM proteins, including fibronectin, vitronectin, laminin, and osteopontin [347]. Osteogenic cells attach to these binding motifs using their membrane receptors, termed integrins. Integrin-mediated cell attachment is crucial for physiological and pathological mechanisms, such as embryonic development, maintenance of tissue integrity, circulation, migration and phagocytic activity of leukocytes, wound healing, and angiogenesis. Integrins are obligate heterodimers composed of two distinct glycoprotein subunits and subunits [348]. Integrin subunits cross the plasma membrane with a long extracellular ligand, while generally a

very short domain remains in the cytoplasm. For the integrin family, 18 and 8 subunits have been characterized in mammals until now. Through the combination of these different subunits, 24 distinct integrins can be assembled. A cell can modulate more than one integrin receptor and change its location, thereby modifying its capacity to bind to different protein sequences [332].

As mentioned earlier, adhesion-promoting proteins in blood (e.g., fibronectin, vitronectin, and various collagen types) bind to integrins through an RGD-dependent pathway [347]. But, there are also different domains within these proteins that have the ability to bind to integrins and provoke integrin-mediated cellular signaling cascades. Briefly, integrin-mediated cell attachment to ECM initiate several intracellular events, including protein kinase C and Na^+/H^+ antiporter, phosphoinositide hydrolysis, tyrosine phosphorylation of membranes, and intracellular proteins [349]. These mechanisms result in mitogen-stimulated protein kinase activation by altering the cellular pH and calcium concentration. Thus, intracellular communication is established and the extracellular signal is transmitted to the nucleus. The cell responds to this integrin-mediated signal through migration, proliferation, and differentiation [350]. The response of osteogenic cells to the initial protein layer on the implant surface is very important for the activation of osteoblastic pathways through integrin-mediated signaling, and therefore for optimal osseointegration. Therefore, the development of an implant surface that favors an osteogenic protein conformation on itself has been one of the major areas of implant surface science. In recent decades, various approaches have focused on understanding the effect of the surface characteristics of the protein-dependent mechanisms of cell adhesion, proliferation, differentiation, and bone matrix deposition, aiming at the development of novel implant surfaces [351,352].

When a biomaterial is inserted into a living body, it absorbs proteins before cells adhere to its surface; once attached to the material's surface, proteins can mediate cell–implant interactions [353,354]. Cells, such as osteoblasts and fibroblasts, mainly interact with the adsorbed proteins, rather than with the implant material itself. For such cells, the implant's surface charge influences their reactions to the implant, by affecting the type and amount of proteins attached on its surface [355].

Summarizing what we have been discussing so far, characteristics of implant surfaces affecting the osteogenic responses are as seen in Figure 11.1.

11.5.1 Collagen Coating

Collagen, as a major constituent of human connective tissues, has been regarded as one of the most important biomaterials. Kim et al. [356] investigated the fibrillar self-assembly of collagen by incubating acid-dissolved collagen in an ionic-buffered medium at 37°C. It was reported that (i) the degree of assembly was varied with the incubation time and monitored by the turbidity change, (ii) the partially assembled collagen contained fibrils with varying diameters, as well as nonfibrillar aggregates, while the fully assembled collagen showed the complete formation of fibrils with uniform diameters of approximately 100–200 nm with periodic stain patterns within the fibrils, which are typical of native collagen fibers,

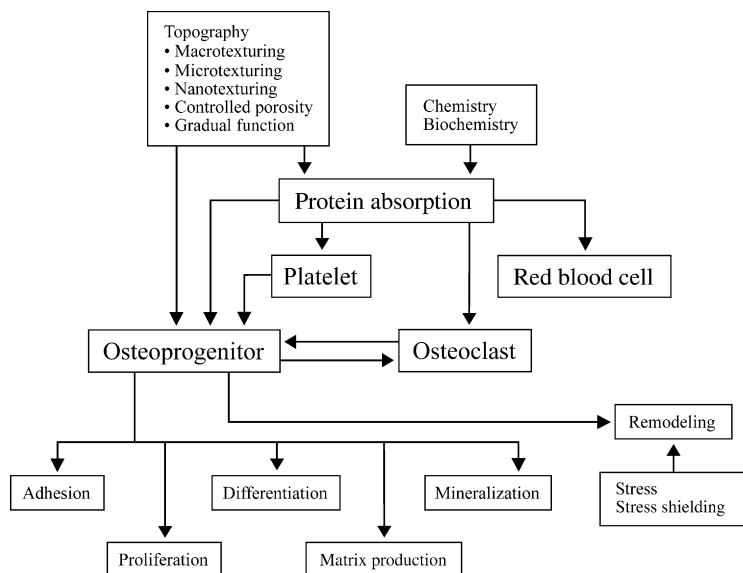


Figure 11.1 Effect of surface characteristics of the implant on the osteogenic response.

and (iii) without the assembly, the collagen layer on Ti adversely affected the cell attachment and proliferation [356].

Frosch et al. [357] evaluated the partial surface replacement of a knee with stem cell–coated titanium implants for a successful treatment of large osteochondral defects. MSCs were isolated from bone marrow aspirates of adult sheep. Round titanium implants were seeded with autologous MSC and inserted into an osteochondral defect in the medial femoral condyle. As controls, defects received either an uncoated implant or were left untreated. Nine animals with 18 defects were sacrificed after 6 months. It was reported that (i) the quality of regenerated cartilage was assessed by *in situ* hybridization of collagen type II and immunohistochemistry of collagen types I and II, (ii) in 50% of the cases, defects treated with MSC-coated implants showed a complete regeneration of the subchondral bone layer, (iii) a total of 50% of MSC-coated and uncoated implants failed to osseointegrate, and formation of fibrocartilage was observed, and (iv) untreated defects, as well as defects treated with uncoated implants, demonstrated incomplete healing of subchondral bone and formation of fibrous cartilage. It was therefore concluded that in a significant number of cases, a partial joint resurfacing of the knee with stem cell–coated titanium implants occurs, and a slow bone and cartilage regeneration and an incomplete healing in half of the MSC-coated implants are limitations of the presented method [357].

Morra et al. [358] evaluated the surface chemistry and the microhardness at the implant–bone interface using a recently developed collagen-coated titanium implant in a short-term rabbit model. Surface chemistry was evaluated by XPS,

while *in vivo* studies involved 4-week implants mid-diaphysis in the lateral femurs of adult male rabbits. After conventional embedding and evaluation of histologic sections, the resin-embedded blocks containing the implanted screws were used to measure bone hardness by means of an indentation test. It was reported that (i) decomposition of the C1s peak obtained by XPS analysis confirmed that surface-immobilized collagen retained all the molecular features of the control, nonimmobilized reference, and (ii) as to microhardness measurement, newly formed bone at the collagen-coated implant–bone interface was significantly harder than bone at the interface of the uncoated control implant and bone, suggesting that collagen coating significantly improves bone maturation and mineralization at the interface in comparison with uncoated CpTi. It was, therefore, concluded that the microhardness measurement at the bone–implant interface showed that collagen coating can significantly improve bone maturation and mineralization at the interface in comparison with uncoated CpTi, confirming and substantiating previous findings by histomorphometric measurements from the same model [358].

The *in vivo* effects of coating titanium implants with organic ECM molecules were examined in the sheep tibia. Titanium screws (5.0 mm) were coated with type I collagen (Ti/Coll) or type I collagen and chondroitin sulfate (Ti/Coll/CS) by biomimetic fibrillogenesis. Uncoated screws (Ti) and screws coated with HA (Ti/HA) served as control. Six adult female sheep received one screw of each type to stabilize a midshaft tibial fracture with external fixation. Four cylindrical implants of 4-mm outer diameter and 3.3-mm inner diameter with the same coatings were inserted into the tibial head. It was found that (i) no pin track infections were seen at the time of implant retrieval 6 weeks after implantation, (ii) extraction torque was greater for Ti/HA (1181 N-mm) and Ti/Coll/CS (1088 N-mm) compared to Ti/Coll (900 N-mm) and Ti (904 N-mm), (iii) newly formed bone was noted around all coated screws within the medullary cavity, (iv) osteoblast activity was significantly increased around loaded Ti/Coll and Ti/Coll/CS screws compared to uncoated Ti screws, and (v) coating of external fixation devices with type I collagen and CS appears to have similar effects as HA with respect to stability and bone healing but with less osteoclast activity [359].

Titanium-based biomaterials for endosseous implants have found widespread applications in the orthopedic, maxillofacial, and dental domains. Indeed, the surface characteristics such as their chemical modification control considerably the cellular response and, subsequently, the quality and the quantity of new-formed bone around the implant. In this study, human osteoprogenitor (HOP) cell adhesion on different titanium surfaces functionalized with HA, type I collagen, or Arg–Gly–Asp (RGD)-containing peptides is investigated by the quartz crystal resonators and by confocal laser scanning microscopy (CLSM) for the imaging of focal contact formation. Data obtained by the quartz crystal resonator technique revealed that RGD-containing peptides alone increase HOP cell adhesion in the early time period of culture. Moreover, association of RGD-containing peptides with either type I collagen or with HA layers induces an additive effect on HOP cell adhesion compared to Ti-Coll or Ti-HA. CLSM shows both the area of focal contact by cell unit and the cytoskeleton network organization to differ according

to the surfaces. Interestingly, association of RGD-containing peptides with HA layers induces an additive effect on focal contact formation on HOP cells compared to Ti–HA alone. It was remarked that the RGD peptide effect occurs in the early time of culture, which is beneficial for osteoblasts with regard to spreading, differentiation, and survival [360].

Collagen/HA nanocomposite thin films containing 10, 20, and 30 wt% HA were prepared on CpTi substrates by the spin coating of their homogeneous sols. All of the nanocomposite coatings having a thickness of $\sim 7.5\ \mu\text{m}$ exhibited a uniform and dense surface, without any obvious aggregation of the HA particles. A minimum contact angle of 36.5° was obtained at 20 wt% HA, suggesting that these coatings would exhibit the best hydrophilicity. The *in vitro* cellular assays revealed that the coating treatment of the Ti substrates favored the adhesion of osteoblast-like cells and significantly enhanced the cell proliferation rate. The cells on the nanocomposite coatings expressed much higher ALP levels than those on the uncoated Ti substrates. Increasing the amount of HA resulted in a gradual improvement in the ALP activity. It was reported that the nanocomposite coatings on Ti substrates also exhibited much better cell proliferation behaviors and osteogenic potentials than the conventional composite coatings with equivalent compositions, demonstrating the greater potential of the former as implant materials for hard tissue engineering [361].

Morra et al. [362] investigated the effect of biochemical surface modification by collagen on the bone response to acid-etched titanium surfaces. Fibrillar type I porcine collagen was adsorbed and covalently linked to acid-etched Ti disks and implants. Adhesion, growth, and specific ALP activity of osteoblast-like SaOS-2 cells were evaluated. Implants in the femur and tibia of rabbit were performed for 2 and 4 weeks and relevant BIC was evaluated by histomorphometry. It was reported that (i) the cell morphology and growth are controlled by the rough acid-etched implants topography, (ii) specific metabolic activity (ALP) is significantly increased by the collagen overlayer, and (iii) importantly, surface modification by collagen increases the speed of peri-implant bone formation, resulting in significantly higher BIC both in femur and tibia at 2 weeks. Based on these findings, it was concluded that morphological (surface topography) and biochemical (surface linking of bioactive molecules) cues can cooperate and yield multifunctional implant surfaces [362].

Biological implant surface coatings are an emerging technology to increase bone formation. Such an approach is of special interest in anatomical regions like the maxilla. Standlinger et al. [363] hypothesized that the coating of titanium implants with components of the organic ECM increases bone formation and implant stability compared to an uncoated reference. The implants were coated using collagen-I with either two different concentrations of CS or two differentially sulfated hyaluronans. Implant coatings were characterized biochemically and with AFM. Histomorphometry was used to assess BIC and bone-volume density (BVD) after 4 and 8 weeks of submerged healing in the maxilla of 20 minipigs. Further, implant stability was measured by resonance frequency analysis (RFA). It was found that (i) implants containing the lower CS concentration had significantly

more BIC, compared to the uncoated reference at both times of interest and (ii) no significant increase was measured from weeks 4 to 8. Differences in BVD and RFA were statistically not significant and (iii) a higher concentration of CS and the application of sulfated hyaluronans showed no comparable increase in BIC. It was concluded that there is a positive effect of a specific collagen-glycosaminoglycan combination on early bone formation *in vivo* [363].

11.5.2 Protein Coating

Titanium surfaces coated with proteins can influence host reactions and thus enhance tissue integration [364]. Fibronectin is a major adhesion protein in the extracellular membrane (matrix)—ECM—and it is important for cell adhesion, migration, proliferation, differentiation, and survival because it facilitates focal contacts with the receptors. Fibronectin is a major ECM protein that is known to promote cell attachment and spreading, differentiation, and phagocytosis. It is a dimeric glycoprotein found in all vertebrates in two forms; soluble (plasma and other fluids) and insoluble (ECM of various tissues). It has a molecular weight between 440 and 500 kDa. Disulfide bridges link one subunit to another via sites near the carboxy-termini of each subunit. The fibronectin protein has folds that lead to structural remodeling and various conformations according to the medium [365,366]. Fibronectin functions in cell adhesion, migration, survival, proliferation, and differentiation as well as tissue organization. The fibronectin can interact with other biomolecules, such as collagen, proteoglycan, heparin, hyaluronic acid, fibrin/fibrinogen, plasma, gangliosides, complement components, and also integral proteins of cell plasma membrane (integrins), as well as with itself [367].

BMPs strongly induce osteogenesis and are enhanced by heparin. Kodama et al. [368] developed a potent osteoinductive material by coating the surface of titanium with AP incorporated with BMP and heparin. Titanium samples were treated with a 5 N NaOH solution and heated at 600°C for 24 h. The treated titanium was soaked in SBF for 4 days and additionally soaked in SBF containing recombinant human BMP2 (rhBMP2; 1000 ng/mL) with or without heparin (30 µg/mL) for 3 days at 37°C. The surfaces of each sample were examined with SEM. The presence of rhBMP2 on the surface of the AP-coated titanium was examined. MC3T3-E1 osteoblast-like cells were cultured on the surface of each sample. The number and morphology of the adherent cells, ALP activity, and OC mRNA expression were examined. It was found that (i) AP was formed on the surface of alkaline heat-treated titanium after soaking in SBF for 7 days, (ii) the presence of rhBMP2 was confirmed by the distribution of BMP-positive immunogold particles, and (iii) the incorporation of (≥ 3 µg/mL) heparin significantly increased ALP activity and OC mRNA expression in the cells on AP-coated titanium containing rhBMP2. It was therefore concluded that heparin enhanced BMP2-induced osteogenesis on AP-coated titanium without the loss of BMP2 activity, and the combination of BMP2 and heparin was effective even in the thin AP layer formed on titanium using the alkaline heat treatment method [368].

Joint replacements should be firmly anchored in vital bone to avoid early implant subsidence and late aseptic loosening. Baas et al. [369] investigated whether the fixation of orthopedic implants could be improved by adding an osteoinductive extract of lyophilized equine bone matrix proteins (Colloss E, Ossacur AG, Germany), between the implant and the surrounding bone. Eighteen uncemented HA-coated implants were inserted pairwise in the proximal tibia of nine dogs. All implants were surrounded by a 2 mm concentric defect. In each dog, the intervention implant was added—20 mg protein lyophilisate. The contralateral control implant was inserted untreated. It was reported that (i) after 4 weeks, the treated HA-coated implants had better mechanical fixation than the untreated control implants, (ii) the treated implants were better osseointegrated, there was more newly formed bone around these implants, and fibrous tissue was eliminated, and (iii) the mechanical implant fixation had a strong positive correlation to new bone formation on and around the implant, and a strong negative correlation to fibrous tissue encapsulation. Based on these findings, it was suggested that bone protein extracts such as the Colloss E device may augment early implant fixation of even HA-coated Ti implants and thereby reduce the risk of long-term failure. This may be particularly useful in revision arthroplasty with bone loss [369].

11.5.3 *Peptide Coating*

Enhanced adhesion and migration of osteoblastic cells on a titanium (Ti) surface is believed to increase the success rate of implant therapy. A GRGDSP peptide derived from fibronectin was coated on Ti surfaces using a tresyl chloride activation technique, and then MC3T3-E1 osteoblastic cells were cultured on the Ti surfaces. It was reported that (i) after 15 days, total RNA was isolated from the cells and gene expression level were analyzed by Affymetrix GeneChip system, (ii) the expression levels of many genes in MC3T3-E1 cells cultured on GRGDSP-coated Ti surface were altered when compared to uncoated Ti, and (iii) in particular, the elevated mRNA levels of BSP and OC were successfully confirmed by RT-PCR and real-time PCR. It was concluded that GRGDSP-coated Ti presented the potential of evolving into a useful biomaterial for successful implant therapy [370]. Bioactive molecules have been proposed to promote beneficial interactions at bone—implant interfaces for enhancing integration. Dettin et al. [371] developed novel methods to functionalize oxidized titanium surfaces by the covalent immobilization of bioactive peptides, through selective reaction involving single functional groups. In the first protocol, an aminoalkylsilane was covalently linked to the Ti oxide layer, followed by covalent binding of glutaric anhydride to the free NH_2 groups. The carboxylic group of glutaric anhydride was used to condense the free N-terminal group of the side-chain protected peptide sequence. Finally, the surface was treated with trifluoroacetic acid to deprotect side-chain groups. In the second protocol, the peptide was directly anchored to the Ti oxide surface via UV activation of an arylazide peptide analogue. XPS analyses confirmed that modifications induced onto surface composition were in agreement with the reactions performed. The peptide density of each biomimetic surface was determined on the basis of

radiolabeling and XPS-derived reaction yields. The *in vitro* cellular response of the biomimetic surfaces was evaluated using a primary human osteoblast cell model. Cell adhesion, proliferation, differentiation, and mineralization were examined at initial-, short-, and long-time periods. It was shown that the biomimetic surface obtained through photoprobe-marked analogue that combines an easily performed modification provides a favorable surface for an enhanced cellular response [371]. Multiform coated titanium implants are widely used in orthopedic and dental surgery. Kokkonen et al. [372] investigated the reactivity of pectin-coated titanium samples implanted under the *latissimus dorsi* muscle fascia of rats. Samples were coated with two enzyme-treated apple pectins—modified hairy regions (MHR-A and MHR-B) that differed in chemical structure. Aminated (AMI) and uncoated titanium (Ti) served as controls. The thicknesses of the peri-implant fibrous tissue capsules formed 1 or 3 weeks after implantation were measured as indicative of possible inflammatory reactions toward the biomaterials. It was found that (i) after 1 week, the MHR-B implant was surrounded by a thicker fibrous capsule (42.9 μm) than any of the other sample types: MHR-A (33.2 μm), AMI (32.5 μm), and Ti (32.3 μm), the last one being the only statistically significant difference, (ii) after 3 weeks, however, this difference disappeared; the capsule thicknesses around MHR-B and Ti implants had decreased to the values found for AMI and MHR-A, and (iii) additionally, the capsule formation represents merely a stromal rather than an inflammatory reaction, as indicated by the absence of activated macrophages or foreign body giant cells in the capsules. It was therefore concluded that, for the first time, the *in vivo* tolerability of covalently linked pectins was indicated and the feasibility of pectin-coated bone and dental implants for clinical use was suggested [372].

11.5.4 CHI Coating

Since bacterial infections associated with implants remain a major cause of their failure, this study investigated the use of polyelectrolyte multilayers (PEMs) comprising hyaluronic acid (HA) and CHI to confer antibacterial properties on titanium (Ti). HA and CHI were deposited on Ti using the layer-by-layer deposition method. The antibacterial efficacy of the functionalized Ti substrates was assessed using *Escherichia coli* and *Staphylococcus aureus*. The number of adherent bacteria on Ti functionalized with HA and CHI PEMs was up to an order of magnitude lower than that on the pristine Ti. The effects of chemical cross-linking of the PEMs on the structural stability and antibacterial efficacy were investigated. The chemical cross-linking of the PEMs imparts greater structural stability and preserves the antibacterial properties even after prolonged immersion in PBS. The cytotoxicity of the PEMs to osteoblasts was evaluated using the MTT assay. The results showed that the biocompatible and long-lasting antibacterial nature of the functionalized Ti substrates offers great potential for reducing implant-associated infections [373]. Circulating progenitor cells are known to home to various organs to repair injured tissues or to routinely replace old cells and maintain tissue integrity. Similarly, circulating progenitor bone cells can possibly home to a bone implant, differentiate,

and eventually osteointegrate with the prosthesis. Osteointegration of bone cells with the prosthesis can help to reduce the risk of implant failure due to constant movement between bone tissue and the implant surface. Lim et al. [374] investigated whether immobilized BMP2 on CHI-grafted titanium substrate (Ti-CS-BMP2) will enhance bone marrow-derived mesenchymal stem cell (BMMSC) adhesion onto the substrate surface and further induce their differentiation into osteoblasts. The results show that Ti-CS-BMP2 substrate is able to retain adsorbed BMP2, and is capable of slow release of this growth factor. Despite the lesser number of BMMSCs initially attached onto the Ti-CS-BMP2 substrates, and consequently the lower level of cell proliferation, Ti-CS-BMP2 cells had the highest level of ALP activity. RT-PCR results show that Ti-CS-BMP2 cells had a relatively higher level of transcription activity of Runx2, compared with that of bone cell-derived osteoblasts (BC-OB), an indication that the BMMSCs were actively differentiating into osteoblasts. Finally, alizarin red staining reveals the presence of calcium deposits in the differentiated cells. It was hence concluded that Ti-CS-BMP2 substrates possess an osteoconductive effect and can possibly be used to fabricate bone implants that can osteointegrate with host bone tissue [374].

The microstructure and wettability of titanium (Ti) surfaces directly impact osteoblast differentiation *in vitro* and *in vivo*. These surface properties are important variables that control initial interactions of an implant with the physiological environment, potentially affecting osseointegration. Park et al. [375] utilized polyelectrolyte thin films to examine how surface chemistry modulates the response of human MG63 osteoblast-like cells to surface microstructure. Three polyelectrolytes—CHI, PGA, and PLL—were used to coat Ti substrates with two different microtopographies (PT, Sa: 0.37 μm and SBA, Sa: 2.54 μm). The polyelectrolyte coatings significantly increased wettability of PT and SBA without altering microscale roughness or morphology of the surface. Enhanced wettability of all coated PT surfaces was correlated with increased cell numbers, whereas cell number was reduced on coated SBA surfaces. ALP-specific activity was greater on coated SBA surfaces than on uncoated SBA, whereas no differences in enzyme activity were seen on coated PT compared to uncoated PT. Culture on CHI-coated SBA enhanced OC and osteoprotegerin production. Integrin expression on smooth surfaces was sensitive to surface chemistry but microtexture was the dominant variable in modulating integrin expression on SBA. These results suggest that surface wettability achieved using different thin films has a major role in regulating osteoblast response to Ti, but this is dependent on the microtexture of the substrate [375].

Parathyroid hormone (PTH) is a well-known therapeutic agent for osteoporosis treatment; however, the inconvenience of daily administration and side effects from systematic administration severely limit its application in clinic. PTH has been incorporated into a biomimetic calcium phosphate (Ca-P) coating via a coprecipitation method in a modified SBF. Yu et al. [376] evaluated the osteointegration response of PTH incorporated Ca-P coating on titanium implants. Implants with different doses of PTH were inserted into tibiae of mice and evaluated by X-ray, micro-CT, histology, and backscattered SEM. It was reported that (i) improved osteointegration of the implants loaded with PTH was observed, compared to Ca-P

coating only after 28 days of implantation in mouse tibiae, (ii) micro-CT analyses showed better bone integration around the implant incorporated with PTH, (iii) BA and bone contact evaluations have demonstrated that peri-implant bone regeneration is highly dependent on the dosage of PTH incorporated, and (iv) the higher the PTH content, the more bone formed surrounding the implant. It was, therefore, concluded that biomimetic Ca-P coating could be a useful a carrier for PTH local delivery, which results in improved bone-to-implant integration [376].

11.6 Coloring

In order to color titanium, there are basically four different methods available: (1) thermal-oxidation, (2) chemical-oxidation, (3) anodic oxidation, and (4) nitriding. By either method the color can be well defined by the thickness of the film (mainly TiO_2) formed on the Ti substrate surface. The color is sometimes referred to as the interference color, which can repeatedly appear under the integral of the half-wave length of the light [377]. Hence, colors, such as rainbow colors, are not colors *per se*. This is true for the first three methods but for the nitriding method, gold is the color of the reaction product (i.e., TiN) and silver is the color of Ti_2N .

As the result of anodization (electrolyte: $\text{H}_3\text{PO}_4\text{:H}_2\text{SO}_4\text{:H}_2\text{O}$ by 8:1:1 ratio), CpTi was covered with anodic oxide film as follows: silver (2 V, 25 Å film thickness), light gold (4 V, 105 Å), gold (12 V, 270 Å), golden violet (20 V, 272 Å), dark blue (24 V, 364 Å), and light blue (30 V, 610 Å). When CpTi (grade II), Ti–6Al–4V, and TiNi were heated in air for 30 min at different temperatures, different interference colors were obtained as seen in Table 11.1, due to different oxide film thicknesses (accordingly, different interference index) [Oshida Y. Unpublished data, 2012]. Since an oxide film formed on titanium substrate becomes colorful, there are several types of colored titanium accessories on the market. If monochromatic light falls normally on a film-covered metal, some being reflected at the film–air interface, some being refracted by the film, and reflected from the metal–oxide interface, interference occurs when the film thickness is proportional to the wavelength of the light. When white light falls on the thin film, interference of certain wavelengths can occur, depending on the film thickness, and the light reaching the eye is colored if the wavelengths subject to interference are within the visible region of the spectrum.

Table 11.1 Summary of Interference Colors, After in-air Oxidation for 30 min

Material	Temperature (°C)				
	350	450	550	650	750
CpTi (II)	Yellowish blue	Brown	Blue	Light green	Bright gray
Ti–6Al–4V	Yellow	Violet	Greenish blue	Bright gray	Light gray
TiNi	Metallic color	Light yellow	Violet	Blue	Reddish violet

Table 11.1 shows such interference colors when CpTi, Ti–6Al–4V, and TiNi coupons are in-air oxidized at various temperatures (resulting in different oxide film thicknesses) at 30 min.

References

- [1] Albrektsson T, Eriksson AR, Friberg B, Lekholm U, Lindahl L, Nevins M, et al. Histologic investigations on 33 retrieved Nobelpharma implants. *Clin Mater* 1993;12:1–9.
- [2] Elias CN, Oshida Y, Lima JHC, Muller CA. Relationship between surface properties (roughness, wettability and morphology) of titanium and dental implant removal torque. *J Mech Behav Biomed Mater* 2008;1:207–74.
- [3] Ramazanoglu M, Oshida Y. Osseointegration and bioscience of implant surfaces—current concepts at bone–implant interface. In: Turkyilmaz I, editor. *Dental Implant/Book I*. InTech Pub.; 2011. p. 57–82.
- [4] Kasemo B, Lausmaa J. Biomaterials and implant surfaces: a surface science approach. *Int J Oral Maxillofac Implants* 1988;3:247–59.
- [5] Baier RE, Meyer AE. Implant surface preparation. *Int J Oral Maxillofac Implants* 1988;3:9–20.
- [6] Reitz WE. The eighth international conference on surface modification technology. *J Met* 1995;47:14–6.
- [7] Smith DC, Pilliar RM, Chernenky R. Dental implant materials I. Some effects of preparative procedures on surface topography. *J Biomed Mater Res* 1991;25:1045–68.
- [8] Buddy D, Ratner B, Thomas JL. Biomaterial surfaces. *J Biomed Mater Res* 1987;21:59–89.
- [9] Ramsden JJ, Allen DM, Stephenson DJ, Alcock JR, Peggs GN, Fuller G, et al. The design and manufacture of biomedical surfaces. *CIRP Ann—Manuf Technol* 2007;56:687–711.
- [10] Guo CY, Tang ATH, Matinlinna JP. Insights into surface treatment methods of titanium dental implants. *J Adhes Sci Technol* 2012;26:189–205.
- [11] Amaral IF, Cordeiro AL, Sampaio P, Barbosa MA. Attachment, spreading and short-time proliferation of human osteoblastic cells and cultured on chitosan films with different degrees of acetylation. *J Biomater Sci Polym Ed* 2007;18:469–85.
- [12] Boyan BD, Hummert YW, Dean DD, Schwarz Z. Role of material surfaces in regulating bone and cartilage cell response. *Biomater* 1996;17:137–46.
- [13] Wael A, Yamada M, Ogawa T. Effect of titanium surface characteristics on the behavior and function of oral fibroblasts. *Int J Oral Maxillofac Implants* 2009;24:419–31.
- [14] Medlin DL, Demkowicz MJ, Marquis EA. Solid state interfaces: toward an atomistic scale understanding of structure, properties, and behavior. *J Met* 2010;62:52.
- [15] Schmitz G, Ene C, Galinski H, Schlesiger R, Stender P. Nanoanalysis of interfacial chemistry. *J Met* 2010;62:58.
- [16] Harimkar SP, Agarwal A, Seal S, Dahotre N. Surface engineering for energy sustainability and bio-applications. *J Met* 2011;63:69.
- [17] Miyakawa O, Watababe K, Okawa S, Shiokawa N, Kobayashi M, Tamura H. Grinding of titanium, part 1: commercial and experimental wheels made of silicon carbide abrasives. *Dent Mater J* 1990;9:30–41.

- [18] Miyakawa O, Watanabe K, Okawa S, Nakano S, Shiokawa N, Kobayashi M, et al. Grinding of titanium, part 2: commercial vitrified wheels made of alumina abrasives. *Dent Mater J* 1990;9:42–52.
- [19] Miyakawa O, Watanabe K, Okawa S, Kanatani M, Nakano S, Kobayashi M. Surface contamination of titanium by abrading treatment. *Dent Mater J* 1996;15:11–21.
- [20] Wen X, Wang X, Zhang N. Microrough surface of metallic biomaterials: a literature review. *Biomed Mater Eng* 1996;6:173–89.
- [21] Piattelli A, Scarano A, Corigliano M, Piattelli M. Presence of multinucleated giant cells around machined, sandblasted and plasma-sprayed titanium implants: a histological and histochemical time-course study in rabbit. *Biomaterials* 1996;17:2053–8.
- [22] Gil FJ, Planell JA, Padrós A, Aparicio C. The effect of shot blasting and heat treatment on the fatigue behavior of titanium for dental implant applications. *Dent Mater* 2007;23:486–91.
- [23] Aparicio C, Gil FJ, Fonseca C, Barbosa M, Planell JA. Corrosion behaviour of commercially pure titanium shot blasted with different materials and sizes of shot particles for dental implant applications. *Biomaterials* 2003;24:263–73.
- [24] Wang CS, Chen KK, Tajima K, Nagamatsu Y, Kakigawa H, Kozono Y. Effects of sandblasting media and steam cleaning on bond strength of titanium–porcelain. *Dent Mater J* 2010;29:381–91.
- [25] Mandelbrot BB. *The fractal geometry of nature*. New York, NY: Freeman; 1983. p. 34.
- [26] Chesters S, Wen HY, Lundin M, Kasper G. Fractal-based characterization of surface texture. *Appl Surf Sci* 1989;40:185–92.
- [27] Sayles RS, Thomas TR. Surface topography as a non-stationary random process. *Nature* 1978;271:431–4.
- [28] Oshida Y, Munoz CA, Winkler MM, Hashem A, Ito M. Fractal dimension analysis of aluminum oxide particle for sandblasting dental use. *J Biomed Mater Eng* 1993;3:117–26.
- [29] Kubo M, Fujishima A, Hotta Y, Kunii J, Shimakura Y, Shimidzu T, et al. Production method of resin-bonded titanium crown by CAD/CAM. In: T. Yoneyama, H. Hamanaka, T. Okuno, editors. 19th Proceedings of the Society of Titanium Research; 2006. p. 42–48.
- [30] Citeau A, Guicheux J, Vinatier C, Layrolle P, Nguyen TP, Pilet P, et al. *In vitro* biological effects of titanium rough surface obtained by calcium phosphate grid blasting. *Biomaterials* 2005;26:157–65.
- [31] Mustafa K, Lopez BS, Hultenby K, Arvison K. Attachment of HGF of titanium surfaces blasted with TiO₂ particles. *J Dent Res* 1997;76:85 [Abstract No. 573].
- [32] Peutzfeld A, Asmussen E. Distortion of alloy by sandblasting. *Am J Dent* 1996;9:65–6.
- [33] Peutzfeld A, Asmussen E. Distortion of alloys caused by sandblasting. *J Dent Res* 1996;75:259 [Abstract No. 1162].
- [34] Miyakawa O, Okawa S, Kobayashi M, Uematsu K. Surface contamination of titanium by abrading treatment. *Dent Indust Jpn* 1998;34:90–6.
- [35] Choi CR, Yu HS, Kim CH, Lee JH, Oh CH, Kim HW, et al. Bone cell responses of titanium blasted with bioactive glass particles. *J Biomater Appl* 2010;25:99–117.
- [36] Jeong R, Marin C, Granato R, Suzuki M, Gil JN, Granjeiro JM, et al. Early bone healing around implant surfaces treated with variations in the resorbable blasting media method. A study in rabbits. *Med Oral Pathol Oral Cir Bucal* 2010;15:e119–25.
- [37] Coelho PG, Lemons JE. Physico/chemical characterization and *in vivo* evaluation of nanothickness bioceramic depositions on alumina-blasted/acid-etched Ti–6Al–4V implant surfaces. *J Biomed Mater Res A* 2009;90:351–61.

- [38] Canabarro A, Diniz MG, Paciornik S, Carvalho L, Sampaio EM, Beloti MM, et al. High concentration of residual aluminum oxide on titanium surface inhibits extracellular matrix mineralization. *J Biomed Mater Res A* 2008;87:588–97.
- [39] Wennerberg A, Albrektsson T, Johnsson C, Andersson B. Experimental study of turned and grit-blasted screw-shaped implants with special emphasis on effects of blasting material and surface topography. *Biomaterials* 1996;17:15–22.
- [40] Johansson CB, Albrektsson T, Thomsen P, Snnerby I, Lodding A, Odelius H. Tissue reactions to titanium–6aluminum–4vanadium alloy. *Eur J Exp Musculoskel Res* 1992;1:161–9.
- [41] Wang CS. Surface modification of titanium for enhancing titanium–porcelain bond strength. Indiana University Master Degree Thesis; 2004.
- [42] Fawzy AS, Amer MA. An *in vitro* and *in vivo* evaluation of bioactive titanium implants following sodium removal treatment. *Den Mater* 2009;25:48–57.
- [43] Zinelis S, Silikas N, Thomas A, Syres K, Eliades G. Surface characterization of SLActive dental implants. *Eur J Esthet Dent* 2012;7:72–92.
- [44] Milleret V, Tugulu S, Schlottig F, Hall H. Alkali treatment of microrough titanium surfaces affects macrophage/monocyte adhesion, platelet activation and architecture of blood clot formation. *Eur Cell Mater* 2011;21:430–44.
- [45] Park JW, Jang IS, Suh JY. Bone response to endosseous titanium implants surface-modified by blasting and chemical treatment: a histomorphometric study in the rabbit femur. *J Biomed Mater Res B Appl Biomater* 2008;84:400–7.
- [46] Stübinger S, Etter C, Miskiewicz M, Homann F, Saldamli B, Wieland M, et al. Surface alterations of polished and sandblasted and acid-etched titanium implants after Er: YAG, carbon dioxide, and diode laser irradiation. *Int J Oral Maxillofac Implants* 2010;25:104–11.
- [47] Pae A, Kim SK, Kim HS, Woo YH. Osteoblast-like cell attachment and proliferation on turned, blasted, and anodized titanium surfaces. *Int J Oral Maxillofac Implants* 2011;26:475–81.
- [48] Oshida Y, Daly J. Fatigue damage evaluation of shot peened high strength aluminum alloy. In: Meguid SA, editor. *Surface engineering*. New York, NY: Elsevier Applied; 1990. p. 404–16.
- [49] Metal Improvement Company, Inc. *Shot peening applications* 7th ed.; 1990.
- [50] DeWald AT, Rankin JE, Hill MR, Lee MJ, Chen HL. Assessment of tensile residual stress mitigation in Alloy 22 welds due to laser peening. *J Eng Mater Tech, Trans ASME* 2004;126:81–9.
- [51] Fairland BP, Wilcox BA, Gallagher WJ, Williams DN. Laser shock-induced microstructural and mechanical property changes in 7075 aluminum. *J Appl Phys* 1972;43:3893–5.
- [52] Fairland BP, Clauer AH. Laser generation of high amplitude stress waves in materials. *J Appl Phys* 1979;50:1497–502.
- [53] Dane CB, Hackel LA, Daly J, Harrison J. High power laser for peening of metals enabling production technology. *Mater Manufac Process* 2000;15:81–96.
- [54] Cho SA, Jung SK. A removal torque of the laser-treated titanium implants in rabbit tibia. *Biomaterials* 2003;24:4859–63.
- [55] Gaggl A, Schultes G, Muller WD, Karcher H. Scanning electron microscopical analysis of laser-treated titanium implants surfaces—a comparative study. *Biomaterials* 2000;21:1067–73.

- [56] Hansson S, Hansson KN. The effect of limited lateral resolution in the measurement of implant surface roughness: a computer simulation. *J Biomed Mater Res* 2005;75A:472–7.
- [57] Endo K. Chemical modification of metallic implant surfaces with biofunctional proteins (Part 1) Molecular structure and biological activity of a modified NiTi alloy surface. *Dent Mater J* 1995;14:185–98.
- [58] Browne M, Gregson PJ. Surface modification of titanium alloy implants. *Biomaterials* 1994;15:894–8.
- [59] MacDonald DE, Deo N, Markovic B, Stranick M, Somasundaran P. Thermal and chemical modification of titanium-aluminum-vanadium implant materials: effects on surface properties, glycoprotein adsorption, and MG63 cell attachment. *Biomaterials* 2004;25:3135–46.
- [60] Park JH, Olivares-Navarrete R, Baier RE, Meyer AE, Tannenbaum R, Boyan BD, et al. Effect of cleaning and sterilization on titanium implant surface properties and cellular response. *Acta Biomater* 2012;8:1966–75.
- [61] Ban S, Iwaya Y, Kono H, Sato H. Surface modification of titanium by etching in concentrated sulfuric acid. *Dent Mater* 2006;22:1115–20.
- [62] Iwaya Y, Mchigashira M, Kanbara K, Miyamoto M, Noguchi K, Izumi Y, et al. Surface properties and biocompatibility of acid-etched titanium. *Dent Mater J* 2008;27:415–21.
- [63] Vanzillotta PS, Sader MS, Bastos IN, Soares GA. Improvement of *in vitro* titanium bioactivity by three different surface treatments. *Dent Mater* 2006;22:275–82.
- [64] Tavares MG, de Oliveira PT, Nanci A, Hawthorne AC, Rosa AL, Xavier SP. Treatment of a commercial, machined surface titanium implant with H_2SO_4/H_2O_2 enhances contact osteogenesis. *Clin Oral Implants Res* 2007;18:452–8.
- [65] Rohanizadeh R, Al-Sadeq M, LeGeros RZ. Preparation of different forms of titanium oxide on titanium surface: effects on apatite deposition. *J Biomed Mater Res* 2004;71A:343–52.
- [66] Ungvári K, Pelsöczy IK, Kormos B, Oszkó A, Rakonczay Z, Kemény L, et al. Effects on titanium implant surfaces of chemical agents used for the treatment of peri-implantitis. *J Biomed Mater Res Part B: Appl Biomater* 2010;94B:222–9.
- [67] Taira Y, Yang L, Atsuta M. Comparison of four fluoride etchants in bonding between titanium and a self-curing luting agent. *Dent Mater J* 2006;25:345–51.
- [68] Ingela U, Petersson IU, Löberg JEL, Fredriksson AS, Ahlberg EK. Semi-conducting properties of titanium dioxide surfaces on titanium implants. *Biomaterials* 2009;30:4471–9.
- [69] Sébastien F, Lamolle SF, Monjo M, Rubert M, Haugen HJ, Lyngstadaas SP, et al. The effect of hydrofluoric acid treatment of titanium surface on nanostructural and chemical changes and the growth of MC3T3-E1 cells. *Biomaterials* 2009;30:736–42.
- [70] Ellingsen JE, Lyngstadaas SP. Increasing biocompatibility by chemical modification of titanium surfaces. In: Ellingsen JE, Lyndstadaas SP, editors. *Bio-implant interface: improving biomaterials and tissue reactions*. 1st ed. Boca Raton, FL: CRC Press; 2003. p. 323–40.
- [71] Ellingsen JE, Birkeland G. The effect on bone healing of fluoride conditioned titanium implants. *J Dent Res* 1996;75:400 [Abstract No. 3060].
- [72] Ellingsen JE. Pre-treatment of titanium implants with fluoride improves their retention in bone. *J Mater Sci: Mater Med* 1995;6:749–58.

- [73] Johansson C, Wennerberg A, Holmén A, Ellingsen JE. Enhanced fixation of bone to fluoride-modified implants. Transaction of the sixth world biomaterials conference. Sydney: Society for Biomaterials; 2002. p. 601.
- [74] He FM, Yang GL, Zhao SF, Cheng ZP. Mechanical and histomorphometric evaluations of rough titanium implants treated with hydrofluoric acid/nitric acid solution in rabbit tibia. *Int J Oral Maxillofac Implants* 2011;26:115–22.
- [75] Daugaard H, Elmengaard B, Bechtold JE, Soballe K. Bone growth enhancement *in vivo* on press-fit titanium alloy implants with acid etched microtexture. *J Biomed Mater Res Part A* 2008;87A:434–40.
- [76] Krozer A, Hall J, Ericsson I. Chemical treatment of machined titanium surfaces. *Clin Oral Implant Res* 1999;10:204–11.
- [77] Rupp F, Scheideler L, Rehbein D, Axmann D, Geis-Gerstorfer J. Roughness induced dynamic changes of wettability of acid etched titanium implant modifications. *Biomaterials* 2004;25:1429–38.
- [78] Kim MH, Lee SY, Kim MJ, Kim SK, Heo SJ, Koak JY. Effect of biomimetic deposition on anodized titanium surfaces. *J Dent Res* 2011;90:711–6.
- [79] Xie L, Liao X, Yin G, Huang Z, Yan D, Yao Y, et al. Preparation, characterization, *in vitro* bioactivity, and osteoblast adhesion of multi-level porous titania layer on titanium by two-step anodization treatment. *J Biomed Mater Res Part A* 2011;98A:312–20.
- [80] Kim KH, Ramaswamy N. Electrochemical surface modification of titanium in dentistry. *Dent Mater J* 2009;28:20–36.
- [81] Yang GL, He FM, Zhao SS, Wang XX, Zhao SF. Effect of H_2O_2/HCl heat treatment of implants on *in vivo* peri-implant bone formation. *Int J Oral Maxillofac Implants* 2008;23:1020–8.
- [82] Yang XF, Chen Y, Yang F, He FM, Zhao SF. Enhanced initial adhesion of osteoblast-like cells on an anatase-structured titania surface formed by H_2O_2/HCl solution and heat treatment. *Dent Mater* 2009;25:473–80.
- [83] Zhang F, Zhang CF, Yin MN, Ren LF, Lin HS, Shi GS. Effect of heat treatment on H_2O_2/HCl etched pure titanium dental implant: an *in vitro* study. *Med Sci Monit* 2012;18:265–72.
- [84] Xiong J, Li Y, Wang X, Hodgson P, Wen C. Mechanical properties and bioactive surface modification via alkali-heat treatment of a porous Ti–18Nb–4Sn alloy for biomedical applications. *Acta Biomater* 2008;4:1963–8.
- [85] Tamilselvi S, Raghavendran HB, Srinivasan P, Rajendran N. *In vitro* and *in vivo* studies of alkali- and heat-treated Ti–6Al–7Nb and Ti–5Al–2Nb–1Ta alloys for orthopedic implants. *J Biomed Mater Res Part A* 2009;90A:380–6.
- [86] Li LH, Kong YM, Kim HW, Kim YW, Kim HE, Heo SJ, et al. Improved biological performance of Ti implants due to surface modification by micro-arc oxidation. *Biomaterials* 2004;15:1867–75.
- [87] Sultana R, Kon M, Hirakata LM, Fujihara E, Asaoka K, Ichikawa T. Surface modification of titanium with hydrothermal treatment at high pressure. *Dent Mater J* 2006;25:470–9.
- [88] Xie Y, Liu X, Huang A, Ding C, Chu PK. Improvement of surface bioactivity on titanium by water and hydrogen plasma immersion ion implantation. *Biomaterials* 2005;26:6129–35.
- [89] Tavares JCM, Cornélio DA, da Silva NB, de Moura CEB, de Queiroz JDF, Sá JC, et al. Effect of titanium surface modified by plasma energy source on genotoxic response *in vitro*. *Toxicology* 2009;262:138–45.

- [90] Gil FJ, Delgado L, Espinar LE, Llamas JM. Corrosion and corrosion-fatigue behavior of cp-Ti and Ti–6Al–4V laser-marked biomaterials. *J Mater Sci Mater Med* 2012;23:885–90.
- [91] Romanos G, Crespi R, Barone A, Covani U. Osteoblast attachment on titanium disks after laser irradiation. *Int J Oral Maxillofac Implants* 2006;21:232–6.
- [92] Somayaji SN, Huet YM, Gruber HE, Hudson MC. UV-killed *Staphylococcus aureus* enhances adhesion and differentiation of osteoblasts on bone-associated biomaterials. *J Biomed Mater Res Part A*. 2010;95A:574–9.
- [93] Ueno T, Yamada M, Hori N, Suzuki T, Ogawa T. Effect of ultraviolet photoactivation of titanium on osseointegration in a rat model. *Int J Oral Maxillofac Implants* 2010;25:287–94.
- [94] Sakamoto H, Hirohasgi Y, Doi H, Tsutsumi Y, Suzuki Y, Noda K, et al. Effect of UV irradiation on the shear bond strength of titanium with segmented polyurethane through γ -mercaptopropyl trimethoxysilane. *Dent Mater J* 2008;27:124–32.
- [95] Ahn UJ, Han JS, Lim BS, Lim YJ. Comparison of ultraviolet light–induced photocatalytic bactericidal effect on modified titanium implant surfaces. *Int J Oral Maxillofac Implants* 2011;26:39–44.
- [96] Park JH, Schwartz Z, Olivares-Navarrete R, Boyan BD, Tannenbaum R. Enhancement of surface wettability via the modification of microtextured titanium implant surfaces with polyelectrolytes. *Langmuir* 2011;27:5976–85.
- [97] Demri B, Hage-Ali M, Moritz M, Muster D. Surface characterization of C/Ti–6Al–4V coating treated with ion beam. *Biomaterials* 1997;18:305–10.
- [98] Poon RWY, Yeung KWK, Liu XY, Chu PK, Chung CY, Lu WW, et al. Carbon plasma immersion ion implantation of nickel-titanium shape memory alloys. *Biomaterials* 2005;26:2265–72.
- [99] Oshida Y, Sachdeva RCL, Miyazaki S. Microanalytical characterization and surface modification of TiNi orthodontic archwires. *J Biomed Mat Eng* 1992;2:51–69.
- [100] Schrooten J, Helsen JA. Adhesion of bioactive glass coating to Ti6Al4V oral implant. *Biomaterials* 2000;21:1419–61.
- [101] Saiz E, Goldman M, Gomez-Vega JM, Tomsia AP, Marshall GW, Marshall SJ. *In vitro* behavior of silicate glass coatings on Ti6Al4V. *Biomaterials* 2002; 23:3749–56.
- [102] Lee JH, Ryu H-S, Lee D-S, Hong KS, Chang B-S, Lee C-K. Biomechanical and histomorphometric study on the bone-screw interface of bioactive ceramic-coated titanium screws. *Biomaterials* 2005;26:3249–57.
- [103] Roriz VM, Rosa AL, Peitl O, Zanutto ED, Panzeri H, DeOliveira PT. Efficacy of a bioactive glass–ceramic (Biosilicate®) in the maintenance of alveolar ridges and in osseointegration of titanium implants. *Clin Oral Implants Res* 2010;21:148–55.
- [104] Mistry S, Kundu D, Datta S, Basu D, Soundrapandian C. Indigenous hydroxyapatite coated and bioactive glass coated titanium dental implant system—Fabrication and application in humans. *J Indian Soc Periodont* 2011;15:215–20.
- [105] Ramaswamy Y, Wu C, Dunstan CR, Hewson B, Eindorf T, Anderson GI, et al. Sphene ceramics for orthopedic coating applications: an *in vitro* and *in vivo* study. *Acta Biomater* 2009;5:3192–204.
- [106] Wang C, Karlis GA, Anderson GI, Dunstan CR, Carbone A, Berger G, et al. Bone growth is enhanced by novel bioceramic coatings on Ti alloy implants. *J Biomed Mater Res Part A* 2009;90A:419–28.
- [107] JETRO. Titanium surface reforming technology. New Technology Japan No. 92-02-100-08. 1992;19:18.

- [108] Bigi A, Boanini E, Bracci B, Faccini A, Panzavolta S, Segatti F, et al. Nanocrystalline hydroxyapatite coatings on titanium: a new fast biomimetic method. *Biomaterials* 2005;26:4085–9.
- [109] Luo P, Nieh TG. Preparing hydroxyapatite powders with controlled morphology. *Biomaterials* 1996;17:1959–64.
- [110] Huang S, Zhou K, Huang B, Li Z, Zhu S, Wang G. Preparation of an electrodeposited hydroxyapatite coating on titanium substrate suitable for *in vivo* applications. *J Mater Sci Mater Med* 2008;19:437–42.
- [111] Tamura M, Endo K, Maida T, Ohno H. Hydroxyapatite film coating by thermally induced liquid-phase deposition method for titanium implants. *Dent Mater J* 2006;25:32–8.
- [112] Liu DM. Fabrication and characterization of porous hydroxyapatite granules. *Biomaterials* 1996;17:1955–7.
- [113] Han Y, Xu K. Photoexcited formation of bone apatite-like coatings on micro-arc oxidized titanium. *J Biomed Mater Res* 2004;71A:608–14.
- [114] Kim HW, Kim HE, Knowles LC. Fluor-hydroxyapatite sol–gel coating on titanium substrate for hard tissue implants. *Biomaterials* 2004;25:3351–8.
- [115] Kim HW, Kim HE, Salih V, Knowles JC. Sol–gel-modified titanium with hydroxyl-apatite thin films and effect on osteoblast-like cell responses. *J Biomed Mater Res* 2005;74A:294–305.
- [116] Kim HW, Koh YH, Li LH, Lee S, Kim HE. Hydroxyapatite coating on titanium substrate with titania buffer layer processed by sol–gel method. *Biomaterials* 2004;25:2533–8.
- [117] Moritz N, Jokinen M, Peltola T, Areva S, Yli-Urpo A. Local induction of calcium phosphate formation on TiO₂ coatings on titanium via surface treatment with a CO₂ laser. *J Biomed Mater Res* 2003;65A:9–16.
- [118] Aksakal B, Hanyaloglu C. Bioceramic dip-coating on Ti–6Al–4V and 316L SS implant materials. *J Mater Sci Mater Med* 2008;19:2097–104.
- [119] Rohanizadeh R, LeGeros RZ, Harsono M, Bendavid A. Adherent apatite coating on titanium substrate using chemical deposition. *J Biomed Mater Res* 2005;72A:428–38.
- [120] Ergun C, Liu H, Halloran JW, Webster TJ. Increased osteoblast adhesion on nano-grained hydroxyapatite and tricalcium phosphate containing calcium titanate *J Biomed Mater Res Part A* 2007;80A:990–7.
- [121] Mano T, Ueyama Y, Ishikawa K, Matsumura T, Suzuki K. Initial tissue response to a titanium implant coated with apatite at room temperature using a blast coating method. *Biomaterials* 2002;23:1931–6.
- [122] Wang X, Li Y, Lin J, Hodgson PD, Wen C. Effect of heat-treatment atmosphere on the bond strength of apatite layer on Ti substrate. *Dent Mater* 2008;24:1549–55.
- [123] Vasanthan A, Kim H, Drukteinis S, Lacefield W. Implant surface modification using laser guided coatings: *in vitro* comparison of mechanical properties. *J Prosthodont* 2008;17:357–64.
- [124] Jonášová L, Müller FA, Helebrant A, Strnad J, Greil P. Hydroxyapatite formation on alkali-treated titanium with different content of Na⁺ in the surface layer. *Biomaterials* 2002;23:3095–101.
- [125] Jonášová L, Müller FA, Helebrant A, Strnad J, Greil P. Biomimetic apatite formation on chemically treated titanium. *Biomaterials* 2004;25:1187–94.
- [126] Wang CX, Wang M, Zhou X. Nucleation and growth of apatite on chemically treated titanium alloy: an electrochemical impedance spectroscopy study. *Biomaterials* 2003;24:3069–77.

- [127] Song W-H, Jun Y-K, Han Y, Hong S-H. Biomimetic apatite coatings on micro-arc oxidized titania. *Biomaterials* 2004;25:3341–9.
- [128] Brinker CJ, Scherer GW. Sol gel science: the physics and chemistry of sol gel processing. San Diego, CA: Academic Press; 1990.
- [129] Hofacker S, Mechtel M, Mager M, Kraus H. Sol gel: a new tool for coatings chemistry. *Prog Organ Coat* 2002;45:159–64.
- [130] Yang YC, Kim K-H, Agrawal CM, Ong JL. Interaction of hydroxyapatite-titanium at elevated temperature in vacuum environment. *Biomaterials* 2004;25:2927–32.
- [131] Brossa F, Cigada A, Chiesa R, Paracchini L, Consonni C. Adhesion properties of plasma sprayed hydroxylapatite coating for orthopaedic prostheses. *J Biomed Mater Eng* 1993;3:127–36.
- [132] Lee EJ, Lee SH, Kim HW, Kong YM, Kim HE. Fluoridated apatite coatings on titanium obtained by electron-beam deposition. *Biomaterials* 2005;26:3843–51.
- [133] Liu H, Jiang W, Malshe A. Novel nanostructured hydroxyapatite coating for dental and orthopedic implants. *J Miner, Met Mater Soc* 2009;61:67–9.
- [134] Daugaard H, Elmengaard B, Bechtold JE, Jensen T, Soballe K. The effect on bone growth enhancement of implant coatings with hydroxyapatite and collagen deposited electrochemically and by plasma spray. *J Biomed Mater Res Part A* 2010;92A:913–21.
- [135] Kang MK, Lee SB, Moon SK, Kim KM, Kim KN. The biomimetic apatite-cefalotin coatings on modified titanium.. *Dent Mater J* 2012;31:98–105.
- [136] Ballo AM, Xia W, Palmquist A, Lindahl C, Emanuelsson L, Lausmaa J, et al. Bone tissue reactions to biomimetic ion-substituted apatite surfaces on titanium implants. *J Roy Soc Interface* 2012;9(72):1615–24.
- [137] Roy M, Bandyopadhyay A, Bose A. Induction plasma sprayed Sr and Mg doped nano hydroxyapatite coatings on Ti for bone implant. *J Biomed Mater Res Part B Appl Biomater* 2011;99B:258–65.
- [138] Lakstein D, Kopelovitch W, Barkay Z, Bahaa M, Hendel D, Eliaz N. Enhanced osseointegration of grit-blasted, NaOH-treated and electrochemically hydroxyapatite-coated Ti–6Al–4V implants in rabbits. *Acta Biomater* 2009;5:2258–69.
- [139] Souto RM, Lemus MM, Reis RL. Electrochemical behavior of different preparations of plasma-sprayed hydroxyapatite coatings on Ti6Al4V substrate. *J Biomed Mater Res* 2004;70A:59–65.
- [140] Filiaggi MJ, Coombs NA, Pilliar RM. Characterization of the interface in the plasma-sprayed HA coating/Ti–6Al–4V implant system. *J Biomed Mater Res* 1991;25:1211–29.
- [141] Yang YC, Chang E, Lee ST. Mechanical properties and Young's modulus of plasma-sprayed hydroxyapatite coating on Ti substrate in simulated body fluid. *J Biomed Mater Res* 2003;67A:886–99.
- [142] Yang YC, Ong JL. Bond strength, compositional, and structural properties of hydroxyapatite coating on Ti, ZrO₂-coated Ti, and TPS-coated Ti substrate. *J Biomed Mater Res* 2003;64A:509–16.
- [143] Filiaggi MJ, Pilliar RM, Coombs NA. Post-plasma-spraying heat treatment of the HA coating/Ti–6Al–4V implant system. *J Biomed Mater Res* 1993;27:191–8.
- [144] Lynn AK, DuQuesnay DL. Hydroxyapatite-coated Ti–6Al–4V Part 2: the effect of post-deposition heat treatment at low temperatures. *Biomaterials* 2002;23:1947–53.
- [145] Yang YC, Chang E. Influence of residual stress on bonding strength and fracture of plasma-sprayed hydroxyapatite coatings on Ti–6Al–4V substrate. *Biomaterials* 2001;22:1827–36.

- [146] Ergun C, Doremus R, Lanford W. Hydroxylapatite and titanium: Interfacial reactions. *J Biomed Mater Res* 2003;65A:336–43.
- [147] Cook SD, Thomas KA, Kay JF, Jarcho M. Hydroxyapatite-coated titanium for orthopedic implant applications. *Clin Orthop* 1988;186:225–43.
- [148] Yang YC, Chang E, Hwang BH, Lee SY. Biaxial residual stress states of plasma-sprayed hydroxyapatite coatings on titanium alloy substrate. *Biomaterials* 2000;12:1327–37.
- [149] Mimura K, Watanabe K, Okawa S, Kobayashi M, Miyakawa O. Morphological and chemical characterizations of the interface of a hydroxyapatite-coated implant. *Dent Mater J* 2004;23:353–60.
- [150] Lynn AK, DuQuesnay DL. Hydroxyapatite-coated Ti–6Al–4V part 1: the effect of coating thickness on mechanical fatigue behaviour. *Biomaterials* 2002;23:1937–46.
- [151] Zavgorodniy AV, Borrero-López O, Hoffman M, LeGeros RZ, Rohanizadeh R. Characterization of the chemically deposited hydroxyapatite coating on a titanium substrate. *J Mater Sci Mater Med* 2011;22:1–9.
- [152] Coelho PG, Cardaropoli G, Marcelo Suzuki M, Lemons JE. Early healing of nanothickness bioceramic coatings on dental implants. An experimental study in dogs. *J Biomed Mater Res Part B: Appl Biomater* 2009;88B:387–93.
- [153] Carrado A. Structural, microstructural, and residual stress investigations of plasma-sprayed hydroxyapatite on Ti–6Al–4V. *ACS Appl Mater Interfaces* 2010;2:561–5.
- [154] Alexander V, Zavgorodniy AV, Borrero-López O, Hoffman M, LeGeros RZ, Rohanizadeh R. Mechanical stability of two-step chemically deposited hydroxyapatite coating on Ti substrate: effects of various surface pretreatments. *J Biomed Mater Res Part B: Appl Biomater* 2011;99B:58–69.
- [155] Porter AE, Taak P, Hobbs LW, Coathup MJ, Blunn GW, Spector M. Bone bonding to hydroxyapatite and titanium surfaces on femoral stems retrieved from human subjects at autopsy. *Biomaterials* 2004;25:5199–208.
- [156] Buser D, Schenk RK, Steinemann S, Fiorelline JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. *J Biomed Mater Res* 1991;25:889–902.
- [157] Ferraris S, Spriano S, Bianchi CL, Cassinelli C, Vernè E. Surface modification of Ti–6Al–4V alloy for biomineralization and specific biological response: part II, alkaline phosphatase grafting. *J Mater Sci Mater Med* 2011;22:1835–42.
- [158] Piattelli A, Trisi P. A light and laser scanning microscopy study of bone/hydroxylapatite-coated titanium implants interface: Histochemical evidence of unmineralized material in humans. *J Biomed Mater Res* 1994;28:529–36.
- [159] Hayashi K, Mashima T, Uenoyama K. The effect of hydroxyapatite coating on bony ingrowth into grooved titanium implants. *Biomaterials* 1999;20:111–9.
- [160] Moroni A, Caja VL, Egger EL, Trinchese L, Chao EYS. Histomorphometry of hydroxyapatite coated and uncoated porous titanium bone implant. *Biomaterials* 1994;15:926–30.
- [161] Thomas KA, Cook SD, Haddad RJ, Kay JF, Jarcho M. Biological response to hydroxyapatite-coated titanium hips. *J Arthrop* 1989;4:43–53.
- [162] Jansen JA, van de Waerden JPCM, Wolke JGC, de Groot K. Histologic evaluation of the osseo adaptation to titanium and hydroxyapatite-coated titanium implants. *J Biomed Mater Res* 1991;25:973–89.
- [163] Gottlander M, Albrektsson T. Histomorphometric studies of hydroxylapatite-coated and uncoated cp titanium threaded implants in bone. *Int J Oral Maxillofac Implants* 1991;6:399–404.

- [164] Schreurs BW, Huiskes R, Buma P, Slooff TJH. Biomechanical and histological evaluation of a hydroxyapatite-coated titanium femoral stem fixed with an intramedullary morsellized bone grafting technique: an animal experiment on goats. *Biomaterials* 1996;17:1177–86.
- [165] Cabrini M, Cigada A, Rondelli G, Vicentini B. Effect of different surface finishing and of hydroxyapatite coatings on passive and corrosion current of Ti6Al4V alloy in simulated physiological solution. *Biomaterials* 1997;18:783–7.
- [166] Hayashi K, Inadome T, Tsumura H, Nakashima Y, Sugioka Y. Effect of surface roughness of hydroxyapatite-coated titanium on the bone–implant interface shear strength. *Biomaterials* 1994;15:1187–91.
- [167] Souto RM, Laz MM, Reis RL. Degradation characteristics of hydroxyapatite coatings on orthopaedic TiAlV in simulated physiological media investigated by electrochemical impedance spectroscopy. *Biomaterials* 2003;24:4213–21.
- [168] Yuda A, Ban S, Izumi Y. Biocompatibility of Apatite-coated titanium mesh prepared by hydrothermal-electrochemical method. *Dent Mater J* 2005;24:588–95.
- [169] Schwartz-Arad D, Mardinger O, Levin L, Kozlovsky A, Hirshberg A. Marginal bone loss pattern around hydroxyapatite-coated versus commercially pure titanium implants after up to 12 years of follow-up. *Int J Oral Maxillofac Implants* 2005; 20:238–44.
- [170] Yang CY, Chen CR, Chang E, Lee TM. Characteristics of hydroxyapatite coated titanium porous coatings on Ti–6Al–4V substrates by plasma sprayed method. *J Biomed Mater Res Part B: Appl Biomater* 2007;82B:450–9.
- [171] Borsari V, Fini M, Giavaresi G, Rimondini L, Consolo U, Chiusoli L, et al. Osteointegration of titanium and hydroxyapatite rough surfaces in healthy and compromised cortical and trabecular bone: *in vivo* comparative study on young, aged, and estrogen-deficient sheep. *J Orthop Res* 2007;25:1250–60.
- [172] Lin A, Wang CJ, Kelly J, Gubbi P, Nishimura I. The role of titanium implant surface modification with hydroxyapatite nanoparticles in progressive early bone–implant fixation *in vivo*. *Int J Oral Maxillofac Implants* 2009;24:808–16.
- [173] Alzubaydi TL, AlAmeer SS, Ismael T, AlHijazi AY, Geetha M. *In vivo* studies of the ceramic coated titanium alloy for enhanced osseointegration in dental applications. *J Mater Sci Mater Med* 2009;20:S35–42.
- [174] Hirota M, Hayakawa T, Ametani A, Kuboki Y, Sato M, Tohnai I. The effect of hydroxyapatite-coated titanium fiber web on human osteoblast functional activity. *Int J Oral Maxillofac Implants* 2011;26:245–50.
- [175] Wennerberg A, Jimbo R, Allard S, Skarnemark G, Andersson M. *In vivo* stability of hydroxyapatite nanoparticles coated on titanium implant surfaces. *Int J Oral Maxillofac Implants* 2011;26:1161–6.
- [176] Kimura I, Kanatani M, Watanabe K. Adhesion of hollow calcium-deficient hydroxyapatite microspheres onto titanium. *Dent Mater J* 2009;28:700–7.
- [177] Moojen DJF, Vogely HC, Fleer A, Nikkels PGJ, Higham PA, Verbout AJ, et al. Prophylaxis of infection and effects on osseointegration using a tobramycin-periapatite coating on titanium implants- An experimental study in the rabbit. *J Orthop Res* 2009;27:710–6.
- [178] Stilling M, Rahbek O, Søballe K. Inferior survival of hydroxyapatite versus titanium-coated cups at 15 years. *Clin Orthop Relat Res* 2009;467:2872–9.
- [179] Sundgren J-E, Bodö P, Lundström I. Auger electron spectroscopic studies of the interface between human tissue and implants of titanium and stainless steel. *J Colloid Interface Sci* 1986;110:9–20.

- [180] Lu X, Leng Y. TEM study of calcium phosphate precipitation on bioactive titanium surfaces. *Biomaterials* 2004;25:1779–86.
- [181] Hanawa T, Ota M. Calcium phosphate naturally formed on titanium in electrolyte solution. *Biomaterials* 1991;12:767–74.
- [182] Li SJ, Yang R, Niinomi M, Hao YL, Cui YY. Formation and growth of calcium phosphate on the surface of oxidized Ti-29Nb-13Ta-4.6Zr alloy. *Biomaterials* 2004;25:2525–32.
- [183] Bogdanski D, Esenwien SA, Prymak O, Eppele M, Muhr G, Köller M. Inhibition of PMN apoptosis after adherence to dip-coated calcium phosphate surfaces on a NiTi shape memory alloy. *Biomaterials* 2004;25:4623–7.
- [184] Kim CS, Ducheyne P. Compositional variations in the surface and interface of calcium phosphate ceramic coatings on Ti and Ti–6Al–4V due to sintering and immersion. *Biomaterials* 1991;12:461–9.
- [185] Ducheyne P, Bianco PD, Kim C. Bone tissue growth enhancement of calcium phosphate coatings on porous titanium alloys: effect of shielding metal dissolution product. *Biomaterials* 1992;13:617–24.
- [186] Krupa D, Baszkiewicz J, Kozubowski JA, Barcz A, Sobczak JW, Biliński A, et al. Effect of dual ion implantation of calcium and phosphorus on the properties of titanium. *Biomaterials* 2005;26:2847–56.
- [187] Fini M, Cigada A, Rondelli G, Chiesa R, Giardino R, Giavaresi G, et al. *In vitro* and *in vivo* behaviour of Ca- and P-enriched anodized titanium. *Biomaterials* 1999;20:1587–94.
- [188] Jansen JA, Hulshoff JE, Van Dijk K. Biological evaluation of thin calcium-phosphate (Ca–P) coatings. *J Dent Res* 1997;76:282 [Abstract No. 2150].
- [189] Hayakawa T, Yoshinari M, Kiba H, Yamamoto H, Nemoto K, Jansen JA. Trabecular bone response to surface roughened and calcium phosphate (Ca–P) coated titanium implants. *Biomaterials* 2002;23:1025–31.
- [190] Barrère F, van der Valk CM, Dalmeijer RAJ, van Blitterswijk CA, de Groot K, Layrolle P. *In vitro* and *in vivo* degradation of biomimetic octacalcium phosphate and carbonate apatite coatings on titanium implants. *J Biomed Mater Res* 2003;64A:378–87.
- [191] Barrère F, Snel MME, van Blitterswijk CA, de Groot K, Layrolle P. Nano-scale study of the nucleation and growth of calcium phosphate coating on titanium implants. *Biomaterials* 2004;25:2901–10.
- [192] Gan L, Wang J, Pilliar RM. Evaluating interface strength of calcium phosphate sol–gel-derived thin films to Ti6Al4V substrate. *Biomaterials* 2005;26:189–96.
- [193] Choi J, Bogdanski D, Köller M, Esenwein SA, Müller D, Eppele M. Calcium phosphate coating of nickel-titanium shape-memory alloys, coating pressure and adherence of leukocytes and platelets. *Biomaterials* 2003;24:3689–96.
- [194] Fend B, Weng J, Yang BC, Qu SX, Zhang XD. Characterization of titanium surfaces with calcium and phosphate and osteoblast adhesion. *Biomaterials* 2004;25:3421–8.
- [195] Lui Q, Ding J, Mante FK, Wunder SL, Baran GR. The role of surface functional groups in calcium phosphate nucleation on titanium foil: a self-assembled monolayer technique. *Biomaterials* 2002;23:3103–11.
- [196] Peng P, Kumar S, Voelcker NH, Szili E, RStC Smart, Griesser HJ. Thin calcium phosphate coatings on titanium by electrochemical deposition in modified simulated body fluid. *J Biomed Mater Res* 2006;76A:347–55.

- [197] Zhang Q, Leng Y, Xin R. A comparative study of electrochemical deposition and biomimetic deposition of calcium phosphate on porous titanium. *Biomaterials* 2005;26:2857–65.
- [198] Heimann RB, Wirth R. Formation and transformation of amorphous calcium phosphates on titanium alloy surfaces during atmospheric plasma spraying and their subsequent *in vitro* performance. *Biomaterials* 2006;27:823–31.
- [199] Ban S, Maruno S, Iwata H, Itoh H. Calcium phosphate precipitation on the surface HA-G-Ti composite under physiologic conditions. *J Biomed Mater Res* 1994;28:65–71.
- [200] Lucas LC, Ong JL. Post deposition heat treatments of Ca–P coating. *J Dent Res* 1993;71:228 [Abstract No. 998].
- [201] Watanabe K, Hashimoto A, Nomura S, Endo MM, Okawa S, Kanatani M, et al. Surface properties of dental implants (Part 2) surface analysis of the titanium implant extracted from a rat bone. *J Jpn Dent Mater* 2004;23:329–34.
- [202] Kim H, Choi SH, Chung SM, Li LH, Lee IS. Enhanced bone forming ability of SLA-treated Ti coated with a calcium phosphate thin film formed by e-beam evaporation. *Biomed Mater* 2012;5:044106 [Abstract only].
- [203] Saber-Samandari S, Berndt CC, Gross KA. Selection of the implant and coating materials for optimized performance by means of nanoindentation. *Acta Biomater* 2011;7:874–81.
- [204] Yang GL, He FM, Song E, Hu JA, Wang XX, Zhao SF. *In vivo* comparison of bone formation on titanium implant surfaces coated with biomimetically deposited calcium phosphate or electrochemically deposited hydroxyapatite. While the BDCaP coating has weaker bone formation properties. *Int J Oral Maxillofac Implants* 2010;25:669–80.
- [205] Poulos NM, Rodriguez NA, Lee J, Rueggeberg FA, Schüpbach P, Hall J, et al. Evaluation of a novel calcium phosphate-coated titanium porous oxide implant surface: a study in Rabbits. *Int J Oral Maxillofac Implants* 2011;26:731–8.
- [206] de Jonge LT, van den Beucken JJJP, Leeuwenburgh SCG, Hamers AAJ, Wolke JGC, Jansen JA. *In vitro* responses to electrosprayed alkaline phosphatase/calcium phosphate composite coatings. *Acta Biomater* 2009;5:2773–82.
- [207] Murai M, Sato S, Fukase Y, Yamada Y, Komiya K, Ito K. Effects of different sizes of β -tricalcium phosphate particles on bone augmentation within a titanium cap in Rabbit calvarium. *Dent Mater J* 2006;25:87–96.
- [208] El-Ghannam AA. Electrophoretic deposition of bioactive silica-calcium phosphate nanocomposite on Ti–6Al–4V orthopedic implant. *J Biomed Mater Res Part B: Appl Biomater* 2011;99B:369–79.
- [209] Ng BS, Annergren I, Soutar AM, Khor KA, Jarfors AEW. Characterization of a duplex TiO_2/CaP coatings on Ti6Al4V for hard tissue replacement. *Biomaterials* 2005;26:1087–95.
- [210] Knabe C, Berger G, Gildenhaar R, Klar F, Zreiqat H. The modulation of osteogenesis *in vitro* by calcium titanium phosphate coatings. *Biomaterials* 2004;25:4911–9.
- [211] Kim HW, Lee EJ, Jun IK, Kim HE. On the feasibility of phosphate glass and hydroxyapatite engineered coating on titanium. *J Biomed Mater Res* 2005;75A:656–67.
- [212] Yamada K, Imamura K, Itoh H, Iwata H, Maruno S. Bone bonding behavior of the hydroxyapatite containing glass-titanium composite prepared by the Cullet method. *Biomaterials* 2001;22:2207–14.

- [213] Maxian SH, Zawadsky JP, Dunn MG. Mechanical and histological evaluation of amorphous calcium phosphate and poorly crystallized hydroxyapatite coatings on titanium implants. *J Biomed Mater Res* 1993;27:717–28.
- [214] Khor KA, Gu YW, Pan D, Cheang P. Microstructure and mechanical properties of plasma sprayed HA/YSZ/Ti–6Al–4V composite coatings. *Biomaterials* 2004;25:4009–17.
- [215] Gu YW, Khor KA, Pan D, Cheang P. Activity of plasma sprayed yttria stabilized zirconia reinforced hydroxyapatite/Ti–6Al–4V composite coatings in simulated body fluid. *Biomaterials* 2004;25:3177–85.
- [216] Chou BY, Chang E, Yao SY, Chen JM. Phase transformation during plasma spraying of hydroxyapatite-19wt%-zirconia composite coating. *J Amer Ceram Soc* 2002;85:661–9.
- [217] Kasugu T, Yoshida M, Ikushima AJ, Tuchiya M, Kusakari H. Stability of zirconia-toughened bioactive glass–ceramics—*in vivo* study using dogs. *J Mater Sci Mater Med* 1993;4:36–9.
- [218] Takagi M, Mochida M, Uchida N, Saito K, Uematsu K. Filter cake forming and hot isostatic pressing for TZP-dispersed hydroxyapatite composite. *J Mater Sci Mater Med* 1992;3:199–203.
- [219] Li H, Khor KA, Cheang P. Titanium dioxide reinforced by hydroxyapatite coatings deposited by high velocity oxy-fuel (HVOF) spray. *Biomaterials* 2002;23:85–91.
- [220] Gu YW, Tay BY, Lim CS, Yong MS. Biomimetic deposition of apatite coating on surface-modified NiTi alloy. *Biomaterials* 2005;26:6916–23.
- [221] van Walter M, Rüger M, Ragoß C, Steffens GCM, Hollander DA, Paar O, et al. *In vitro* behavior of a porous TiO₂/ perlite composite and its surface modification with fibronectin. *Biomaterials* 2005;26:2813–26.
- [222] Shtansky DV, Gloushankova NA, Sheveiko AN, Kharitonova MA, Moizhess TG, Levashov EA, et al. Design, characterization and testing of Ti-based multi-component coatings for load-bearing medical applications. *Biomaterials* 2005;26:2909–24.
- [223] Chu CL, Chung CY, Zhou J, Pu YP, Lin PH. Fabrication and characteristics of bioactive sodium titanate/titania graded film on NiTi shape memory alloy. *J Biomed Mater Res* 2005;75A:595–602.
- [224] Redepenning J, Venkataraman G, Chen J, Stafford N. Electrochemical preparation of chitosan/hydroxyapatite composite coatings on titanium substrates. *J Biomed Mater Res* 2003;66A:411–6.
- [225] Rodrigues CVM, Serricella P, Linhares ABR, Guerdes RM, Borojevic R, Rossi MA, et al. Characterization of a bovine collagen-hydroxyapatite composite scaffold for bone tissue engineering. *Biomaterials* 2003;24:4987–97.
- [226] Cheng X, Filiaggi M, Roscoe SG. Electrochemically assisted co-precipitation of protein with calcium phosphate coatings on titanium alloy. *Biomaterials* 2004;25:5395–403.
- [227] Venugopalan R, George MA, Weimer JJ, Lucas LC. Surface topography, corrosion and microhardness of nitrogen-diffusion-hardened titanium alloy. *Biomaterials* 1999;20:1709–16.
- [228] Dion I, Rouais F, Trut L, Ch Baquency, Monties JR, Havlik P. TiN coating: surface characterization and haemocompatibility. *Biomaterials* 1993;14:1230–5.
- [229] Oshida Y, Hashem A. Titanium-porcelain system. Part I: Oxidation kinetics of nitrided pure titanium, simulated to porcelain firing process. *J Biomed Mater Eng* 1993;3:185–98.

- [230] Thair L, Kamachi Mudali U, Bhurvaneswaran N, Nair KGM, Asokamani R, Raj B. Nitrogen ion implantation and *in vitro* corrosion behavior of as-cast Ti–6Al–7Nb alloy. *Corr Sci* 2002;44:2439–57.
- [231] Bordji K, Jouzeau JY, Mainard D, Payan E, Netter P, Rie KT, et al. Cytocompatibility of Ti–6Al–4V and Ti–5Al–2.5Fe alloys according to three surface treatments, using human fibroblasts and osteoblasts. *Biomaterials* 1996;17:929–40.
- [232] Goldberg JR, Gilbert JL. The electrochemical and mechanical behavior of passivated and TiN/AlN-coated CoCrMo and Ti6Al4V alloys. *Biomaterials* 2004;25:851–64.
- [233] Tamura Y, Yokoyama A, Watari F, Kawasaki T. Surface properties and biocompatibility of nitrided titanium for abrasion resistant implant materials. *Dent Mater J* 2002;21:355–72.
- [234] Kokubo T, Ito S, Shigematsu M, Sakka S. Fatigue and life-time of bioactive glass–ceramic A-W containing apatite and wollastonite. *J Mater Sci* 1987;22:4067–70.
- [235] Morton PH, Bell T, Weisheit A, Kroll J, Mordike BL, Sagoo K. Laser gas nitriding of titanium and titanium alloys. In: Sudarshan TS, Braza JF, editors. *Surface Modification Technologies V*. The Institute of Materials; 1992. p. 593–609.
- [236] Eberhardt AW, Pandey R, Williams JM, Weimer JJ, Ila D, Zimmermann RL. The role of residual stress and surface topography on hardness of ion implanted Ti–6Al–4V. *Mater Sci Eng* 1997;A229:147–55.
- [237] Shetty RH. Mechanical and corrosion properties of nitrogen diffusion hardened Ti–6Al–4V alloy ASTM STP 1272 In: Brown SA, Lemons JE, editors. *Medical applications of titanium and its alloys: the material and biological issues*. American Society for Testing and Materials; 1996. p. 240–51.
- [238] Semlitsch MF, Weber H, Streicher RM, Schon R. Joint replacement components made of hot-forged and surface-treated Ti–6Al–7Nb alloy. *Biomaterials* 1992;13:781–8.
- [239] Thull R. Semiconductive properties of passivated titanium and titanium based hard coatings on metals for implants—an experimental approach. *Med Prog Technol* 1990;16:225–34.
- [240] Wisbey A, Gregson PJ, Tuke M. Application of PVD TiN coating to Co–Cr–Mo-based surgical implants. *Biomaterials* 1987;8:477–80.
- [241] Venugopalan R, Weimer JJ, George MA, Lucas LC. The effect of nitrogen diffusion hardening on the surface chemistry and scratch resistance of Ti–6Al–4V alloy. *Biomaterials* 2000;21:1669–77.
- [242] Cyster LA, Parker KG, Parker TL, Grant DM. The effect of surface chemistry and nanotopography of titanium nitride (TiN) films on primary hippocampal neurons. *Biomaterials* 2004;25:97–107.
- [243] Bull SJ, Chalker PR. The role of titanium interlayers in the adhesion of titanium nitride thin films The Institute of Materials In: Sudarshan TS, et al., editors. *Surface Modification Technologies*. Cambridge: The University Press; 1992. p. 205–15.
- [244] Oshida Y, Fung LW, Ishikbay SC. Titanium-porcelain system. Part II: bond strength of fired porcelain on nitrided pure titanium. *J Biomed Mater Eng* 1997;7:13–34.
- [245] Głuszek J, Jedrokwiaak J, Markowski J, Masalski J. Galvanic couples of 316L steel with Ti and ion plated Ti and TiN coatings in Ringer's solutions. *Biomaterials* 1990;11:330–5.

- [246] da Silva JSP, Amico SC, Rodrigues AON, Barboza CAG, Alves Jr C, Croci AT. Osteoblastlike cell Adhesion on titanium surfaces modified by Plasma Nitriding. *Int J Oral Maxillofac Implants* 2011;26:237–44.
- [247] Brama M, Rhodes N, Hunt J, Ricci A, Teghil R, Migliaccio S, et al. Effect of titanium carbide coating on the osseointegration response *in vitro* and *in vivo*. *Biomaterials* 2007;28:595–608.
- [248] Zhu Y, Watari F. Surface carbonization of titanium for abrasion-resistant implant materials. *Dent Mater J* 2007;26:245–53.
- [249] Lee B-H, Kim JK, Kim YD, Choi K, Lee KH. *In vivo* behavior and mechanical stability of surface-modified titanium implants by plasma spray coating and chemical treatments. *J Biomed Mater Res* 2004;69A:279–85.
- [250] Sonoda T, Kotake S, Kakimi H, Yamada M, Naganuma K, Kato M, et al. On the dental application of titanium-base alloy. Part 7: Titanium coating by sputtering. *Gov Ind Res Inst* 1991;40:291–9.
- [251] Sonoda T, Kotake S, Kakimi H, Yamada M, Naganuma M, Kato M, et al. On the dental application of titanium-base alloy. Part 8: Pure titanium coating on the denture base of Ti–6Al–4V alloy by sputtering. *Gov Indust Res Inst* 1991;40:300–7.
- [252] Smith T. The effect of plasma-sprayed coatings on the fatigue of titanium alloy implants. *J Met* 1994;46:54–6.
- [253] Gruen TA, McNeice GM, Amstutz HD. Models of failure: cemented stem-type femoral components—a radiographic analysis of loosening. *Clin Orthop* 1979;141:17–27.
- [254] Willert HG, Ludwig J, Semlitsch M. Reaction of bone to methacrylate after hip arthroplasty: a long-term gross, light microscopic and scanning electron microscopic study. *J Bone Joint Surg* 1974;56A:1368–73.
- [255] Smith TS. Rationale for biological fixation of prosthetic devices. *SAMPE J* 1985;21(33):14–6.
- [256] Engh CA, Bobyn JD. Biologic fixation of hip prosthesis: a review of the clinical status and current concepts. *Adv Orthop Surg* 1984;18:136–49.
- [257] Reclaru L, Eschler P-Y, Lerf R, Blatter A. Electrochemical and metal ion release from Co–Cr–Mo prosthesis with titanium plasma spray coating. *Biomaterials* 2005;26:4747–56.
- [258] Ku CH, Pioletti DP, Browne M, Gregson PJ. Effect of different Ti–6Al–4V surface treatments on osteoblasts behaviour. *Biomater* 2002;23:1447–54.
- [259] Cai Z, Nakajima H, Woldu M, Berglund A, Bergmann M, Okabe T. *In vitro* corrosion resistance of titanium made using different fabrication methods. *Biomaterials* 1999;20:183–90.
- [260] Chen G, Wen Z, Zhang N. Corrosion resistance and ion dissolution of titanium with different surface microroughness. *Biomed Mater Res* 1998;8:61–74.
- [261] Head WC, Mallory TH, Emerson RH. The proximal porous coating alternative for primary total hip arthroplasty. *Orthopedics* 1999;22:813–5.
- [262] Bourne RB, Rorabeck CH, Burkart BC, Kirk PG. Ingrowth surfaces-plasma sprayed coating to titanium alloy hip replacements. *Clin Orthop Rel Res* 1994;298:37–46.
- [263] Reclaru L, Lerf R, Eschler P-Y, Blatter A, Meyer J-M. Evaluation of corrosion on plasma sprayed and anodized titanium implants, both with and without bone cement. *Biomaterials* 2003;24:3027–38.
- [264] Xue W, Liu X, Zheng XB, Ding C. *In vivo* evaluation of plasma-sprayed titanium coating after alkali modification. *Biomaterials* 2005;26:3029–37.

- [265] Borsari V, Giavaresi G, Fini M, Torricelli P, Tschon M, Chiesa R, et al. Comparative *in vitro* study on a ultra-high roughness and dense titanium coating. *Biomaterials* 2005;26:4948–55.
- [266] Vercaigne S, Wolke JBC, Naert I, Jansen JA. The effect of titanium plasma-sprayed implants on trabecular bone healing in the goat. *Biomaterials* 1998;19:1093–9.
- [267] Ong JL, Carnes DL, Bessho K. Evaluation of titanium plasma-sprayed and plasma-sprayed hydroxyapatite implants *in vivo*. *Biomaterials* 2004;25:4601–6.
- [268] Brems J, Steinhäuser E, Paulus G. Commercially pure titanium Steinäuser plate-screw system for maxillofacial surgery. *Biomaterials* 1988;9:310–3.
- [269] Rae T. A study on the effects of particulate metals of orthopaedic interest on murine macrophages *in vitro*. *J Bone Jt Surg Br* 1975;57:444–50.
- [270] Rae T. The toxicity of metals used in orthopaedic prostheses. An experimental study using cultured human synovial fibroblasts. *J Bone Jt Surg Br* 1981;63-B:435–40.
- [271] Brune D, Evje D, Melson S. Corrosion of gold alloys and titanium in artificial saliva. *Scand J Dent Res* 1982;90:168–71.
- [272] Franchi M, Bacchelli B, Martini D, DePasquale V, Orsini E, Ottani V, et al. Early detachment of titanium particles from various different surfaces of endosseous dental implants. *Biomaterials* 2004;25:2239–46.
- [273] Han CM, Kim HE, Kim YS, Han SK. Enhanced biocompatibility of Co–Cr implant material by Ti coating and micro-arc oxidation. *J Biomed Mater Res Part B: Appl Biomater* 2009;90:165–70.
- [274] Wazen RM, Lefebvre LP, Baril E, Nanci A. Initial evaluation of bone ingrowth into a novel porous titanium coating. *J Biomed Mater Res Part B: Appl Biomater* 2010;94B:64–71.
- [275] Pan J, Leygraf C, Thierry D, Ektessabi AM. Corrosion resistance for biomaterial applications of TiO₂ films deposited on titanium and stainless steel by ion-beam-assisted sputtering. *J Biomed Mater Res* 1997;35:309–18.
- [276] New Technology Japan. Ti–O coating in Ti–6Al–4V alloy by DC reactive sputtering method. *JETR* 1994;22:18.
- [277] Gluszek J, Masalski J, Furman P, Nitsch K. Structural and electrochemical examinations of PACVD TiO₂ films in Ringer solution. *Biomaterials* 1997;18:789–94.
- [278] De Aza PN, Guitian F, De Aza S. Reactivity of wollastonite-tricalcium phosphate bioeutectic ceramic in human parotid saliva. *Biomaterials* 2000;21:1735–41.
- [279] Siriphannon P, Hayashi S, Yasumori A, Okada K. Preparation and sintering of CaSiO₃ from coprecipitated powder using NaOH as precipitant and its apatite formation in simulated body fluid solution. *J Mater Res* 1999;14:529–36.
- [280] Lui X, Ding C. Plasma sprayed wollastonite/TiO₂ composite coatings on titanium alloys. *Biomaterials* 2002;23:4065–77.
- [281] Fraichinger VM, Schlottig F, Gasser B, Textor M. Anodic plasma-chemical treatment of CP titanium surfaces for biomedical applications. *Biomaterials* 2004;25:593–606.
- [282] Haddow DB, Kothari S, James PF, Short RD, Hatton PV, van Noort R. Synthetic implant surfaces 1. The formation and characterization of sol–gel titania films. *Biomaterials* 1996;17:501–7.
- [283] Sato M, Slamovich EB, Webster TJ. Enhanced osteoblast adhesion on hydrothermally treated hydroxyapatite/titania/poly(lactide-co-glycolide) sol–gel titanium coatings. *Biomaterials* 2005;26:1347–9.
- [284] Wang X-X, Hayakawa S, Tsuru K, Osaka A. Bioactive titania gel layers formed by chemical treatment of Ti substrate with a H₂O₂/HCl solution. *Biomaterials* 2002;23:1353–7.

- [285] Manjubala I, Kumar TSS. Effect of TiO_2 – Ag_2O additives on the formation of calcium phosphate based functionally graded bioceramics. *Biomaterials* 2000;21:1995–2002.
- [286] Nonami T, Taoda H, Hue NT, Watanabe E, Iseda K, Tazawa M, et al. Apatite formation on TiO_2 photocatalyst film in a pseudo body solution. *Mater Res Bull* 1998;33:125–31.
- [287] Shibata Y, Kawai H, Yamamoto H, Igarashi T, Miyazaki T. Antibacterial titanium plate anodized by being discharged in NaCl solution exhibits cell compatibility. *J Dent Res* 2004;83:115–9.
- [288] Popescu S, Demetrescu I, Sarantopoulos C, Gleizes AN, Iordachescu D. The biocompatibility of titanium in a buffer solution: compared effects of a thin film of TiO_2 deposited by MOCVD and of collagen deposited from a gel. *J Mater Sci Mater Med* 2007;18:2075–83.
- [289] Zhou XS, Li LJ, Lin YH, Nan CW. Characterization and properties of anatase TiO_2 film prepared via colloidal sol method under low temperature. *J Electroceramics* 2008;21:795–7.
- [290] Cui X, Kim HM, Kawashita M, Wang L, Xiong T, Kokubo T, et al. Preparation of bioactive titania films on titanium metal via anodic oxidation. *Dent Mater* 2009;25:80–6.
- [291] Narayan RJ, Monteiro-Riviere NA, Brigmon RL, Pellin MJ, Elam JW. Atomic layer deposition of TiO_2 thin films on nanoporous alumina templates: medical applications. *JOM J Miner, Met Mater Soc* 2009;61:12–6.
- [292] Zhang Z, Sun J, Hu H, Wang Q, Liu X. Osteoblast-like cell adhesion on porous silicon-incorporated TiO_2 coating prepared by micro-arc oxidation. *J Biomed Mater Res Part B: Appl Biomater* 2011;97:224–34.
- [293] Ääritalo V, Areva S, Jokinen M, Mika Lindén, Peltola T. Sol–gel-derived TiO_2 – SiO_2 implant coatings for direct tissue attachment. Part I: design, preparation and characterization. *J Mater Sci Mater Med* 2007;18:1863–73.
- [294] Hu H, Zhang W, Qiao Y, Jiang X, Liu X, Ding C. Antibacterial activity and increased bone marrow stem cell functions of Zn-incorporated TiO_2 coatings on titanium. *Acta Biomater* 2012;8:904–15.
- [295] Yamamoto O, Alvarez K, Kikuchi T, Fukuda M. Fabrication and characterization of oxygen-diffused titanium for biomedical applications. *Acta Biomater* 2009;5:3605–15.
- [296] Tanaka Y, Watanabe I, Okabe T. Cross-sectional TEM analysis of porcelain fused to gold-coated titanium. *Dent Mater J* 2007;26:84–8.
- [297] Tran PA, Sarin L, Hurt RH, Webster TJ. Differential effects of nanoselenium doping on healthy and cancerous osteoblasts in coculture on titanium. *Int J Nanomedicine* 2010;5:351–8.
- [298] Krishna BV, Xue W, Bose S, Bandyopadhyay A. Functionally graded Co–Cr–Mo coating on Ti–Al–4V alloy structures. *Acta Biomater* 2008;4:697–706.
- [299] Suh JY, Jeung OC, Choi BJ, Park JW. Effects of a novel calcium titanate coating on the osseointegration of blasted endosseous implants in rabbit tibiae. *Clin Oral Implants Res* 2007;18:362–9.
- [300] Brunot C, Grosgeat B, Picart C, Lagneau C, Jaffrezic-Renault N, Ponsonnet L. Response of fibroblast activity and polyelectrolyte multilayer films coating titanium. *Dent Mater* 2008;24:1025–35.
- [301] Agarwal A, Dahotre NB. Laser surface engineering of titanium diboride coatings. *Adv Mater Process* 2000;158:43–5.

- [302] Brånemark PI. Osseointegration and its experimental background. *J Prosthet Dent* 1983;50:399–410.
- [303] Albrektsson T, Johansson C. Osteoinduction, osteoconduction and osseointegration. *Eur Spine J* 2001;10:96–101.
- [304] Albrektsson T, Hansson HA, Ivarsson B. Interface analysis of titanium and zirconium bone implants. *Biomaterials* 1985;6:97–101.
- [305] Albrektsson T, Jansson T, Lekholm U. Osseointegrated dental implants. *Dent Clinics of North America* 1986;30:151–74.
- [306] Eisenbarth E, Velten D, Müller M, Thull R, Breme J. Biocompatibility of beta-stabilizing elements of titanium alloys. *Biomaterials* 2004;25:5705–13.
- [307] Hallab NJ, Skipor A, Jacobs JJ. Interfacial kinetics of titanium- and cobalt-based implant alloys in human serum: metal release and biofilm formation. *J Biomed Mater Res Part A* 2003;65:311–8.
- [308] Stanford CM, Keller JC. The concept of osseointegration and bone matrix expression. *Critical Rev Oral Biology Med* 1991;2:83–101.
- [309] Stanford CM. Surface modification of biomedical and dental implants and the processes of inflammation, wound healing and bone formation. *Int J Mol Sci* 2010;11:354–69.
- [310] Henry PJ, Laney WR, Jemt T, Harris D, Krogh PH, Polizzi G, et al. Osseointegrated implants for single-tooth replacement: a prospective 5-year multicenter study. *Int J Oral Maxillofac Implants* 1996;11:450–5.
- [311] Jemt T, Chai J, Harnett J, Heath MR, Hutton JE, Johns RB, et al. 5-year prospective multicenter follow-up report on overdentures supported by osseointegrated implants. *Int J Oral Maxillofac Implants* 1996;11:291–8.
- [312] Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II). Etiopathogenesis. *Eur J Oral Sci* 1998;106:721–64.
- [313] Morton D, Bornstein MM, Wittneben JG, Martin WC, Ruskin JD, Hart CN, et al. Early loading after 21 days of healing of nonsubmerged titanium implants with a chemically modified sandblasted and acid-etched surface: two-year results of a prospective two-center study. *Clin Implant Dent Relat Res* 2010;12:9–17.
- [314] Ramazanoglu M, Lutz R, Ergun C, von Wilmowsky C, Nkenke E, Schlegel KA. The effect of combined delivery of rhBMP-2 and rhVEGF165 from biomimetic Ca–P coated implants on osseointegration. *Clin Oral Implants Related Res* 2011;22:1433–9.
- [315] von Wilmowsky C, Bauer S, Lutz R, Meisel M, Neukam FW, Toyoshima T, et al. *In vivo* evaluation of anodic TiO₂ nanotubes: an experimental study in the pig. *J Biomed Mater Res Part B: Appl Biomater* 2009;89:165–71.
- [316] Mendonça G, Mendonça DB, Aragão FJ, Cooper LF. Advancing dental implant surface technology—from micron- to nanotopography. *Biomaterials* 2008;29:3822–35.
- [317] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones; toward a morphological compatibility of implants. *Biomed Mater Eng* 1994;4:397–407.
- [318] Oshida Y. Requirements for successful biofunctional implants. *Int Symp Adv Biomater* 2000;5.
- [319] Oshida Y, Tuna EB, Aktoren A, Gencay K. Dental Implant Systems. *Int J Mol Sci* 2010;11:1580–678.
- [320] Oshida Y. Bioscience and bioengineering of titanium materials. 1st ed. Oxford, UK: Elsevier; 2007.

- [321] Oshida Y, Tuna EB. Science and technology integrated titanium dental implant systems. In: Basu B, Katti DS, Kumar A, editors. Advanced biomaterials. John Wiley & Sons; 2009. p. 143–77.
- [322] Davies JE. Understanding peri-implant endosseous healing. J Dent Educ 2003;67:932–49.
- [323] Kuzyk PR, Schemitsch EH. The basic science of peri-implant bone healing. Indian J Orthop 2011;45:108–15.
- [324] Osborn JF. Biomaterials and their application to implantation. SSO Schweiz Monatsschr für Zahn 1979;89:1138–9.
- [325] Kienapfel H, Sprey C, Wilke A, Griss P. Implant fixation by bone ingrowth. J Arthroplasty 1999;14:355–68.
- [326] Zhao X, Liu X, Ding C. Acid-induced bioactive titania surface. J Biomed Mater Res Part A 2005;75:888–94.
- [327] Kilpadi KL, Chang PL, Bellis SL. Hydroxyapatite binds more serum proteins, purified integrins, and osteoblast precursor cells than titanium or steel. J Biomed Mater Res 2001;57:258–67.
- [328] Hench LL, Wilson J. Surface-active biomaterials. Science 1984;226:630–6.
- [329] Davies JE. *In vitro* modeling of the bone/implant interface. The Anatomical Record 1996;245:426–45.
- [330] Adell R, Lekholm U, Rockler B, Branemark PIA. 15-year study of osseointegrated implants in the treatment of the edentulous jaw. Int J Oral Surg 1981;10:387–416.
- [331] Marco F, Milena F, Gianluca G, Vittoria O. Peri-implant osteogenesis in health and osteoporosis. Micron 2005;36:630–44.
- [332] Dee KC, Puleo DA, Bizios R. An introduction to tissue-biomaterial interactions. Hoboken, NJ: John Wiley & Sons; 2002. p. 3–15.
- [333] Dereka XE, Markopoulou CE, Vrotsos IA. Role of growth factors on periodontal repair. Growth Factors 2006;24:260–7.
- [334] Heldin CH, Westermarck B. Mechanism of action and *in vivo* role of platelet-derived growth factor. Physiological Rev 1999;79:1283–316.
- [335] Schliephake H. Bone growth factors in maxillofacial skeletal reconstruction. Int J Oral Maxillofac Surg 2002;31:469–84.
- [336] Meyer U, Joos U, Mythili J, Stamm T, Hohoff A, Fillies T, et al. Ultrastructural characterization of the implant/bone interface of immediately loaded dental implants. Biomaterials 2004;25:1959–67.
- [337] Park JY, Davies JE. Red blood cell and platelet interactions with titanium implant surfaces. Clin Oral Implants Res 2000;11:530–9.
- [338] Puleo DA, Nanci A. Understanding and controlling the bone–implant interface. Biomaterials 1999;20:2311–21.
- [339] Klinger MM, Rahemtulla F, Prince CW, Lucas LC, Lemons JE. Proteoglycans at the bone–implant interface. Crit Rev Oral Biology Med 1998;9:449–63.
- [340] Chappard D, Aguado E, Huré G, Grizon F, Basle MF. The early remodeling phases around titanium implants: a histomorphometric assessment of bone quality in a 3- and 6-month study in sheep. Int J Oral Maxillofac Implants 1999;14:189–96.
- [341] Kasemo B, Lausmaa J. Biomaterial and implant surfaces: on the role of cleanliness, contamination, and preparation procedures. J Biomed Mater Res 1988;22:145–58.
- [342] Kasemo B, Gold J. Implant surfaces and interface processes. Advances Dent Res 1999;13:8–20.
- [343] Lim YJ, Oshida Y. Initial contact angle measurements on variously treated dental/medical titanium materials. Biomed Mater Eng 2001;11:325–41.

- [344] Park BS, Heo SJ, Kim CS, Oh JE, Kim JM, Lee G, et al. Effects of adhesion molecules on the behavior of osteoblast-like cells and normal human fibroblasts on different titanium surfaces. *J Biomed Mater Res Part A* 2005;74:640–51.
- [345] Yang Y, Cavin R, Ong JL. Protein adsorption on titanium surfaces and their effect on osteoblast attachment. *J Biomed Mater Res Part A* 2003;67:344–9.
- [346] Lee MH, Oh N, Lee SW, Leesungbok R, Kim SE, Yun YP, et al. Factors influencing osteoblast maturation on microgrooved titanium substrata. *Biomaterials* 2010;31:3804–15.
- [347] Ruoslahti E. RGD and other recognition sequences for integrins. *Ann Rev Cell Dev Biol* 1996;12:697–715.
- [348] Hynes RO. Integrins: bidirectional, allosteric signaling machines. *Cell* 2002;110:673–87.
- [349] Plopper GE, McNamee HP, Dike LE, Bojanowski K, Ingber DE. Convergence of integrin and growth factor receptor signalling pathways within focal adhesion complex. *Mol Biology of the Cell* 1995;6:1349–65.
- [350] Sawyer AA, Hennessy KM, Bellis SL. Regulation of mesenchymal stem cell attachment and spreading on hydroxyapatite by RGD peptides and adsorbed serum proteins. *Biomaterials* 2005;26:1467–75.
- [351] Schwartz Z, Kieswetter K, Dean DD, Boyan BD. Underlying mechanisms at the bone-surface interface during regeneration. *J Periodontal Res* 1997;32:166–71.
- [352] Colnot C, Romero DM, Huang S, Rahman J, Currey JA, Nanci A, et al. Molecular analysis of healing at a bone–implant interface. *J Dent Res* 2007;86:862–7.
- [353] Andrade JD. Principles of protein adsorption. In: Andrade JD, editor. *Surface and interfacial aspects of biomedical polymers*. New York, NY: Plenum Press; 1985. p. 1–80.
- [354] Brash JL, Horbett TA. Protein at interfaces: current issues and future prospects. In: Brash JL, Horbett TA, editors. *Proteins at interfaces: physicochemical and biomechanical studies*. Washington, DC: ACS; 1987. p. 1–33.
- [355] Hing KA. Bone repair in the twenty-first century: biology, chemistry or engineering?. *Phil Trans Roy Soc* 2004;362:2821–50.
- [356] Kim HW, Li LH, Lee EJ, Lee SH, Kim HE. Fibrillar assembly and stability of collagen coating on titanium for improved osteoblast responses. *J Biomed Mater Res* 2005;75A:629–38.
- [357] Frosch K-H, Drengk A, Krause P, Viereck V, Miosge N, Werner C, et al. Stem cell-coated titanium implants for the partial joint resurfacing of the knee. *Biomaterials* 2006;27:2542–9.
- [358] Morra M, Cassinelli C, Meda L, Fini M, Giavaresi G, Giardino R. Surface analysis and effects on interfacial bone microhardness of collagen-coated titanium implants: a rabbit model. *Int J Oral Maxillofac Implants* 2005;20:23–30.
- [359] Rammelt S, Heck C, Bernhardt R, Bierbaum S, Scharnweber D, Goebbels J, et al. *In vivo* effects of coating loaded and unloaded Ti implants with collagen, chondroitin sulfate, and hydroxyapatite in the sheep tibia. *J Orthop Res* 2007;25:1052–61.
- [360] Le Guillou-Buffello D, Bareille R, Gindre M, Sewing A, Laugier P, Amédée J. Additive effect of RGD coating to functionalized titanium surfaces on human osteoprogenitor cell adhesion and spreading. *Tissue Eng Part A* 2008;14:1445–55.
- [361] Teng SH, Lee EJ, Park CS, Choi WY, Shin DS, Kim HE. Bioactive nanocomposite coatings of collagen/hydroxyapatite on titanium substrates. *J Mater Sci Mater Med* 2008;19:2453–61.

- [362] Morra M, Cassinelli C, Cascardo G, Bollati D, Rodriguez R. Multifunctional implant surfaces: surface characterization and bone response to acid-etched Ti implants surface-modified by fibrillar collagen I. *J Biomed Mater Res* 2010;94:271–9.
- [363] Stadlinger B, Hintze V, Bierbaum S, Möller S, Schulz MC, Mai R, et al. Biological functionalization of dental implants with collagen and glycosaminoglycans-A comparative study. *J Biomed Mater Res B Appl Biomater* 2011;21:331–41.
- [364] Scheideler I, Rupp F, Wendel H, Sathe S, Gerstorfer J. Photocoupling of fibronectin to titanium surfaces influences keratinocyte adhesion, pellicle formation and thrombogenicity. *Dent Mater* 2007;23:469–78.
- [365] Park J, Koak J, Jang J, Han C, Kim S, Heo S. Osseointegration of anodized titanium implants coated with fibroblast growth factor-fibronectin (FGF-FN) fusion protein. *Int J Oral Maxillofac Implants* 2006;21:859–66.
- [366] Antia M, Baneyx G, Kubow KE, Vogel V. Fibronectin in aging extracellular matrix fibrils is progressively unfolded by cells and elicits an enhanced rigidly response. *Faraday Discuss* 2008;139:229–49.
- [367] Miyamoto S, Katz BZ, Lafrenie RM, Yamada KM. Fibronectin and integrins in cell adhesion, signaling, and morphogenesis. *Ann NY Acad Sci* 1998;857:119–29.
- [368] Kodama T, Goto T, Miyazaki T, Takahashi T. Bone formation on apatite-coated titanium incorporated with bone morphogenetic protein and heparin. *Int J Oral Maxillofac Implants* 2008;23:1013–9.
- [369] Baas J, Jakobsen T, Elmengaard B, Bechtold JE, Soballe K. The effect of adding an equine bone matrix protein lyophilisate on fixation and osseointegration of HA-coated Ti implants. *J Biomed Mater Res Part A* 2012;100:188–94.
- [370] Yamamichi N, Pugdee K, Chang WJ, Lee SY, Yoshinari M, Hayakawa T, et al. Gene expression monitoring in osteoblasts on titanium coated with fibronectin-derived peptide. *Dent Mater J* 2008;27:744–50.
- [371] Dettin M, Herath T, Gambaretto R, Iucci G, Battocchio C, Bagno A, et al. Assessment of novel chemical strategies for covalent attachment of adhesive peptides to rough titanium surfaces: XPS analysis and biological evaluation. *J Biomed Mater Res* 2009;91:463–79.
- [372] Kokkonen H, Niiranen H, Schols HA, Morra M, Stenbäck F, Tuukkanen J. Pectin-coated titanium implants are well-tolerated *in vivo*. *J Biomed Mater Res* 2010;93:1404–9.
- [373] Chua PH, Neoh KG, Shi Z, Kang ET. Structural stability and bioapplicability assessment of hyaluronic acid–chitosan polyelectrolyte multilayers on titanium substrates. *J Biomed Mater Res* 2008;87:1061–74.
- [374] Lim TY, Wang W, Shi Z, Poh CK, Neoh KG. Human bone marrow-derived mesenchymal stem cells and osteoblast differentiation on titanium with surface-grafted chitosan and immobilized bone morphogenetic protein-2. *J Mater Sci Mater Med* 2009;20:1–10.
- [375] Park JH, Olivares-Navarrete R, Wasilewski CE, Boyan BD, Tannenbaum R, Schwartz Z. Use of polyelectrolyte thin films to modulate osteoblast response to microstructured titanium surfaces. *Biomaterials* 2012;33:5267–77.
- [376] Yu X, Wang L, Jiang X, Rowe D, Wei M. Biomimetic CaP coating incorporated with parathyroid hormone improves the osseointegration of titanium implant. *J Mater Sci Mater Med* 2012;23 [Abstract only].
- [377] Evans UR. *Metallic corrosion passivity and protection*. London: Edward Arnold; 1937. p. 672–81.

12 Advanced Materials, Technologies, and Processes

12.1 Introduction

Before we discuss the new and interesting things ahead of us, it is appropriate timing here to review what has happened in the past and what is happening currently. Titanium materials science is a typical interdisciplinary (or transdisciplinary, in the sense of dissecting preexisting disciplines and compiling them to create a new field of) science and engineering. Figure 12.1 illustrates the complicated yet nicely correlated interrelationship among different disciplines to establish a promising titanium materials science and engineering for assisting not only industry but also health providers as well as the receiver of such services. In Figure 12.1, in order for engineered titanium materials to serve as titanium biomaterials, we have been discussing and reviewing numerous articles to prove that appropriate surface modifications and characterizations should be properly preformed and accurately reflected to fabrication technologies and methods. Then such titanium biomaterials are really ready to be used in different dental and medical applications. We have reviewed the ever-growing Ti materials research and development for meeting specific aims including V-free alloys, β -Ti alloys, Ti materials having better properties of fatigue as well as wear, amorphatizable materials, materials exhibiting better superplastic formability, and macro-, micro-, and nanoscale structure-controlled surface-textured materials. These new Ti materials, along with conventional Ti materials, are characterized to evaluate whether they meet specific required characteristics. All these activities, as seen in the figure, are nicely correlated to establish titanium biomaterials from which various dental and medical applications can be realized. Furthermore, currently and continuously in the future, with tremendous valuable and supportive technologies (including newly developed surface modification, near-net shape (NNS) forming, better understating of bone healing mechanisms, advanced tissue engineering (TE) materials and technologies, etc.) implant systems can be further developed to bring benefits to both patients and dental/medical clinicians.

Biomaterial science comprises elements of medicine, biology, chemistry, TE, and, above all, materials science. Research activities are aimed at understanding of the fundamental relationships between material properties and the biomedical applications of materials, taking into account specific applications of materials and also essential requests that determine the choice of those materials.

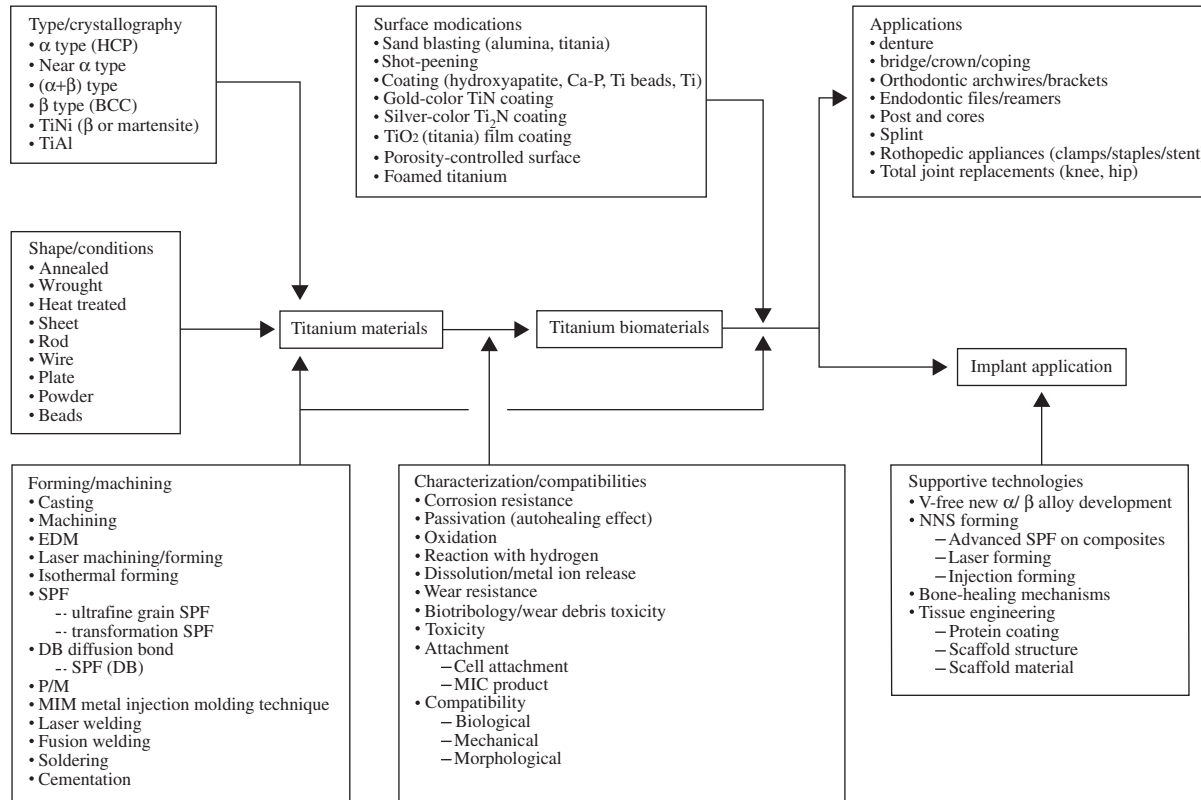


Figure 12.1 Interacting map of various disciplines involved in titanium materials.

In the past, when tissues became diseased or damaged, a physician had little recourse but to remove the offending part, with obvious limitations. Removal of joints, vertebrae, teeth, or organs led to only a marginally improved quality of life. However, human survivability seldom exceeded the progressive decrease in quality of tissues, and so the need for replacement parts was small. During the last century the situation changed greatly. The discovery of antiseptics, penicillin and other antibiotics, chemical treatment of water supplies, improved hygiene, and vaccination all contributed to a major increase in human survivability in developed countries. Life expectancy is now in the range of $80 +$ years. In the past, it was the major practice to remove the diseased tissues, whereas at present, either transplants (using autografts, heterografts, or homografts) or implants (using biological fixation, bioactive fixation, or cement fixation) are commonly utilized, and in the future, regeneration of tissues, based on engineered tissues and regenerative bioactive materials, will have a major clinical impact. Regeneration of tissues means the following: (1) restoration of structure, (2) restoration of function, (3) restoration of metabolic and biochemical behavior, and (4) restoration of biomechanical performance. Our challenge for the future is to extend these findings to studies in compromised bones with osteopenia and osteoporosis, to apply the findings to larger animals, and especially humans, with aging bones, and to use the findings to design the 3D architectures required for engineering of tissues [1]. Based on what we have seen so far, we can see further research and development in materials, technology, engineering, and clinical applications to provide better health services in the coming years, particularly characterized by an ever-aging society.

In this chapter, among many future perspectives associated with medical and dental as well as industry, biomaterials development and related technologies will be revealed.

12.2 Materials, Structures, and Processes

Most of the titanium biomaterials in all phase classifications are currently clinical or experimentally employed, as described in Chapter 2. Here, amorphatized materials, glassy metals, sponge-like structures, and new concept to fabricate TiNi alloy structure will be reviewed. Amorphous (or glassy) metal systems have been extensively studied since their introduction for their unique structural, mechanical, electronic, magnetic, and corrosion properties. The amount of crystallographic damage can be enough to completely amorphize the surface of the target: that is, it can become an amorphous solid (such a solid produced from a melt is called a glass). In some cases, complete amorphatization of a target is preferable to a highly defective crystal. If the number of generated point defects is very high, a crystalline material undergoes a phase transition to an amorphous state where neither a long-range nor a short-range order of the atoms can be found [2–5].

TiAl amorphous alloy provides high strength, linear elastic behavior, and the infinite fatigue life necessary for high device reliability. This alloy was originally

developed useful for material for the digital micromirror device chip and possesses actually a TiAl_3 phase [6]. Bulk amorphous Ti-based alloys were found to be formed in the diameter range up to 5 mm for the Ti–Ni–Cu–Sn and Ti–Ni–Cu–Si–B systems, which possess a high glass-forming ability [7]. There are newly reported Ti45–Ni20–Cu25–Sn5–Zr5 [8], Ti50–Cu20–Ni24–Si4–B2 [9] and Ti–Cu [10] that can be amorphatized. These alloys can be produced by such techniques as liquid quenching, molecular deposition, or external action, and they retain a disordered structure resembling the liquid. As such, they have no long-range order. There is, however, short-range order over a few atomic distances (as found in the liquid state). Recently, medium-range order has been investigated. This has prompted the use of the terms glassy or vitreous to distinguish them from materials that are truly amorphous on the atomic scale.

Accumulative roll bonding (ARB) is a severe plastic deformation (SPD) process to fabricate ultrafine grained metallic materials. ARB is the only SPD process applicable to continuous production of bulky materials. In this process, 50% rolled material is cut into two, stacked to be the initial dimension, and then rolled again. In order to obtain one-body solid material, the rolling in ARB is not only a deformation process but also a bonding process (roll bonding). By repeating this procedure, SPD of bulky materials can be realized [11–13]; hence, a similar technology to the mechanical alloying can be found.

A multielementary Ti–10Zr–5Nb–5Ta alloy, with nontoxic alloying elements, was used to develop an ARB in order to improve its structural and mechanical properties. The alloy was obtained by a cold crucible semi-levitation melting technique and then was ARB processed. After three ARM cycles, the total deformation degree per layer is about 86%; the calculated medium layer thickness is about 13 μm . It was reported that (i) the ARB-processed alloy has a low elastic modulus of 46 GPa, a value close to the value of the natural cortical bone (about 20 GPa), (ii) ultimate tensile strength obtained for ARB-processed alloy is rather high, suitable to be used as a material for bone substitute, and (iii) hardness of the ARB-processed alloy is higher than that of the as-cast alloy, ensuring a better behavior as an implant material. It was further found that (i) corrosion behavior of the studied alloy revealed the improvement of the main electrochemical parameters, as a result of the positive influence of ARB processing and (ii) lower corrosion and ion release rates for the ARB-processed alloy than for the as-cast alloy due to the favorable effect of ARB thermomechanical processing were obtained [14].

Kishi [15] developed a unique 3D metallic fiber structure. Vertical nickel fiber and horizontal Ti fiber were 3D woven and the mechanically woven 3D structure was heat treated to allow all contact points between Ni and Ti wires to achieve a solid-state diffusion bonding. Depending on prefabricating 3D network, the porosity can be controlled between 40% and 95%. Moreover, the uniqueness of this technology is that diffusion-bonded contact points (with a huge number of contact points) can behave as TiNi alloy, exhibiting shape memory effect and/or superelasticity after subsequent heat treatments.

The first titanium sponge was developed ([http://www.eurocoating.it/plasma + -spray + coatings/growth/default.aspx](http://www.eurocoating.it/plasma+-spray+coatings/growth/default.aspx)) to be applicable to prostheses made with

thermal spray technology. It consists of open and interconnected large size pores arranged in a titanium matrix. The pore and interconnected channel size range is between 100 and 800 μm . With open interconnected porosities up to 800 μm in diameter, it has been proven to be, unique, and new solution for spraying a metallic trabecular structure onto medical implants. Conventional cementless endosseous prostheses are generally made of titanium alloys and are supplied with a surface roughened by sandblasting, plasma spray coating, etching, etc. These surfaces, while biocompatible, allow bone apposition only. State-of-the-art wide porous networks are created and applied to prostheses using complex post processes. The unique aspect of this newly developed titanium sponge is that while designed to bring about bone ingrowth due to its large pores, it can also be easily and quickly applied to all prosthetic surfaces ([http://www.eurocoating.it/plasma + spray + coatings/growth/default.aspx](http://www.eurocoating.it/plasma+spray+coatings/growth/default.aspx)).

Bones made of titanium was reported (<http://www.asminternational.org/portal/site/mpmd/News>; <http://www.LayerWise.com>). Objects are made by 3D printing (3DP) ultrathin layers of a material on top of each other until a desired finished product is made. 3DP is currently moving from conventional industrial applications toward medical uses. Titanium bones can now be printed and put into the body. This was recently done for a Belgian woman who was suffering from oral cancer and an infection that was eating away her jawbone. Their process of 3DP is called metal additive manufacturing. First, a 3D CAD model is created on a computer and that information is sent to the 3D printer. In this process, titanium powder is put in the enclosed printer. Lasers then melt the powder into thousands of 2D layers until a finished 3D piece is made. It was reported that the patient was able to speak and move her new jaw within hours of the surgery (<http://www.LayerWise.com>).

12.3 Functionally Graded Materials and Design Concept

In materials science, functionally graded material (FGM) may be characterized by the variation in composition and structure gradually over volume, resulting in corresponding changes in the properties of the material. The materials can be designed for specific function and applications. Various approaches based on the bulk (particulate processing), preform processing, layer processing, and melt processing are used to fabricate the FGMs. In a FGM, the properties change gradually with position. The property gradient in the material is caused by a position-dependent chemical composition, microstructure, or atomic order. As early as 1972, the usefulness of functionally graded (FG) composites with a graded structure was reported [16]. Since then, a major part of the research on FGMs was dedicated to the processing of these materials and a large variety of production methods has been developed [17]. The manufacturing process of a FGM can usually be divided into building the spatially inhomogeneous structure (“gradation”) and transformation of this structure into a bulk material (“consolidation”) [18].

Material is composed of multilayers, with each layer having unique characteristics, though adjacent layers have some similarity, is called gradient functional material (GFM). Although such functions can include various properties, the gradient function is limited to mechanical, physical, or thermal properties since other properties, such as chemical or electrochemical, are more likely important to the surface layer and not related to bulky or semi-bulky behavior. For example, if hydroxyapatite is needed to be spray coated onto CpTi, this GFM concept can be applied. Instead of applying HA powder directly onto the CpTi surface, a multilayer of HA/HA + Al₂O₃/Al₂O₃ + TiO₂/TiO₂/CpTi can be prepared to enhance the bonding strength (Y. Oshida, unpublished data, 2012). From the HA side to CpTi side, the mechanical properties (particularly, modulus of elasticity) and thermal properties (such as linear coefficient of thermal expansion) are gradually changing so that when this HA-coated CpTi is subjected to stressing, interfacial stress between each constituent layer can be minimized, with the result that the degree of discreteness in the stress field can also be minimized.

The National Industrial Research Institute of Nagoya of the Agency of Industrial Science and Technology has established technology for forming a gradient functional titanium oxide film on a titanium alloy (Ti–6Al–4V) by the reactive DC sputtering vapor deposition method [19]. The method was developed for fabricating denture bases and artificial implants, and the oxygen concentration was changed continuously during sputtering to provide a gradient in the film composition by which adhesivity to the alloy, surface hardness, and biocompatibility were improved. Denture bases produced by superplastic forming (SPF) are cleaned with an organic solvent, the oxygen concentration is changed continuously during sputtering, and pure titanium is vapor deposited by the reactive DC sputtering. In the initial stage, intermetallic bonding is achieved by oxygen-free vapor deposition, and so the adhesion is excellent and there is no fear of exfoliation. But farther away from the metal surface, the oxygen concentration is raised gradually to form a gradient film. At the surface some titanium oxides are formed. It was reported that (i) titanium oxide features excellent biocompatibility, and since it is a hard material, resists damage and (ii) the overall film thickness in the experimental was 3 μm, and the Vickers hardness of the surface was 1500 (200–300 for pure titanium) [19].

Bogdanski et al. [20] fabricated the FGM, which was prepared through powder metallurgical processing with thoroughly mixed powders of the elements. Ten mixtures were prepared ranging from Ni:Ti of 90:10 (by at.%) through 80:20 to Ni:Ti = 10:90 and pure Ti (0:100). Each mixture was homogenized in a mixer for 24 h in a bottle without addition of grinding balls to keep impurities low. The compaction was done by hot isostatic pressing at 1050°C and 195 MPa for 5 h. It was reported that, using cells (comprised of osteoblast-like osteosarcoma cells, primary human osteoblasts, and murine fibroblasts), good biocompatibility of Ni–Ti alloys has shown up to about 50% Ni [20].

It is well known that the main inorganic component of natural bone is hydroxyapatite (HA) and that the main organic component is collagen. HA implants are not bioabsorbable, and because induction of bone into and around the artificially made

HA is not always satisfactory, loosening or breakage of HA implants may occur during the postimplantation in the clinical application. The development of a new material that is bioabsorbable and has osteoconductive activity is needed. Therefore, the implant was designed, in the presence of cancellous bone as a thin layer around it, from FGM, and a novel biomaterial collagen/HA, as a FGM, was developed using the finite element and optimization techniques. These materials have a self-organized character similar to that of natural bone. The investigations have shown that the maximum stress in the cortical bone and cancellous bone for the collagen/HA FG implant has been reduced by about 40% and 19%, respectively, compared to the currently used titanium dental implants [21].

The thermal–mechanical performance of HA/Ti FG dental implants was studied with the 3D finite element method. The HA/Ti FG dental implant performance is evaluated against the maximum von Mises stress, which is the general performance indicator, the first principal/tensile stress for mechanical failure of implant–bone bond, and the third principal/compressive stress of bone absorption. Simulation results indicate that, under the influence of occlusal force only, the FG implants with different HA fraction along the implant length perform almost equally well, while the titanium implant sustains much higher von Mises stress. However, when thermal stress is also considered, the FG implant having HA fraction exponential index of $m = 2$ with temperature decrease of 20°C yields the highest first principal and von Mises stresses among all the FG and titanium implants [22].

Fracture study was conducted on Ti–6Al–4V implants incorporating a gradient of porosity, from the inner core to the outer case, obtained by laser sintering of metal powder. Surface appearance, microstructure, composition, mechanical properties, and fractography were evaluated. The specimens were prepared by a selective laser sintering procedure using a Ti–6Al–4V alloy powder with a particle size of 1–10 μm . The flexure strength was determined by a three-point bend test. It was reported that the elastic modulus of the inner core material was 104 GPa; while that of the outer porous material was 77 GPa [23].

Implant surfaces were designed to attach less to bone but at the same time improve osseous healing for use as temporary bone fracture plates. The strategy was to combine the nonadhesive properties of smooth titanium (Ti) surfaces with the differentiative and antiinflammatory properties of eicosapentaenoic acid (EPA). Machined Ti implant surfaces coated with a layer of EPA, with or without UV irradiation, were characterized by X-ray photoelectron spectroscopy, and the *in vivo* performance was evaluated in New Zealand White rabbits. The performance of the functionalized implants was analyzed after 10 weeks of healing by mechanical pull-out testing, molecular biology, and histological and microcomputed tomography (μCT) analysis. The results indicate that surface functionalization with UV light can reduce bone attachment and volumetric bone mineral density in the peri-implant bone tissue. The presence of EPA on the surfaces enhanced this effect further. Gene expression of bone formation markers showed a trend toward higher mRNA levels in all EPA-treated groups. The histological analyses demonstrated lower inflammation in the UV-irradiated group and immature bone formation in all the groups. In conclusion, surface functionalization of Ti implants with UV light

and EPA could be a biocompatible coating for reduced bone-bonding ability of Ti while promoting bone formation [24].

Functional gradation is one characteristic feature of living tissue. Bioinspired materials open new approaches for manufacturing implants for bone replacement. Different routes for new implant materials are presented using the principle of functional gradation. An artificial biomaterial for knee joint replacement has been developed by building a graded structure consisting of ultrahigh-molecular weight polyethylene (UHMWPE) fiber-reinforced high-density polyethylene combined with a surface of UHMWPE. The ingrowth behavior of titanium implants into hard tissue can be improved by depositing a graded biopolymer coating of fibronectin, collagen types I and III with a gradation, derived from the mechanisms occurring during healing *in vivo*. FG porous hydroxyapatite ceramics can be produced using alternative routes, for example, sintering of laminated structures of HA tapes filled with polymer spheres or combining biodegradable polyesters such as polylactide and polyglycolide, with carbonated nanocrystalline hydroxyapatite. It was found that HA-collagen I scaffolds are an appropriate material for *in vitro* growth of bone, suggesting that the scaffold has to be FG in order to create an optimized mechanical behavior as well as the intended improvement of the cell ingrowth [25].

Graded functional (GF) design is also important in TE, aiming to create biological substitutes to repair or replace failing organs or tissues due to trauma or aging. One of the more promising approaches in TE is to grow cells on biodegradable scaffolds, which act as temporary supports for the cells to attach, proliferate, and differentiate, after which the scaffold will degrade, leaving behind a healthy regenerated tissue. Tissues in nature, including human tissues, exhibit gradients across a spatial volume, in which each identifiable layer has specific functions to perform so that the whole tissue/organ can behave normally. Such a gradient is termed as a functional gradient. A good TE scaffold should mimic such a gradient, which fulfills the biological and mechanical requirements of the target tissue. Thus, the design and fabrication process of such scaffolds become more complex and the introduction of computer-aided tools will lend themselves well to ease these challenges [26].

12.4 Controlled Porosity/Foamed Structures

12.4.1 Controlled Porosity

As osteoinductive biomaterials contain calcium and phosphorous, the important factors for osteoinduction are thought to be (i) the chemical composition of the biomaterial, (ii) the specific dissolution properties of the biomaterial, and (iii) the surface morphology of the biomaterial acting as a bone substitute should possess osteoconductive and osteoinductive ability and should have superior mechanical properties [27–30].

Selective electron beam melting (EBM) was successfully used to fabricate novel cellular Ti–6Al–4V structures for orthopedic applications. Microcomputer

tomography analysis demonstrated the capability to fabricate 3D structures with an interconnected porosity and pore sizes suitable for tissue ingrowth and vascularization. Mechanical properties, such as compressive strength and elastic modulus, of the tested structures were similar to those of human bone. Thus, stress-shielding effects after implantation might be avoided due to a reduced stiffness mismatch between implant and bone—namely, poor mechanocompatibility. A chemical surface modification using HCl and NaOH induced apatite formation during *in vitro* bioactivity tests in simulated body fluid (SBF) under dynamic conditions. The modified bioactive surface is expected to enhance the fixation of the implant in the surrounding bone as well as to improve its long-term stability [31]. Porous titanium and titanium alloys are promising scaffold biomaterials for bone TE because they have the potential to provide new bone ingrowth abilities and low elastic modulus to match that of natural bone. A new highly porous Ti–6Ta–4Sn alloy scaffold with the addition of biocompatible alloying elements (Ta and Sn) was prepared using a space-holder sintering method. The strength of the Ti–6Ta–4Sn scaffold with a porosity of 75% was found to be significantly higher than that of a pure Ti scaffold with the same porosity. The elastic modulus of the porous alloy can be customized to match that of human bone by adjusting its porosity. In addition, it was reported that the porous Ti–6Ta–4Sn alloy exhibited an interconnected porous structure, which enabled the ingrowth of new bone tissues. Cell culture results revealed that human SaOS₂ osteoblast-like cells grew and spread well on the surfaces of the solid alloy and throughout the porous scaffold. The surface roughness of the alloy showed a significant effect on the cell behavior, and the optimum surface roughness range for the adhesion of the SaOS₂ cell on the alloy was 0.15–0.35 mm. Hence, it was suggested that the porous Ti–6Ta–4Sn alloy scaffold as an orthopedic implant material with a special emphasis on its excellent biomechanical properties and *in vitro* biocompatibility with a high preference by osteoblast-like cells was promising [32].

The surface characteristics and *in vitro* osteoconductivity of a titanium surface incorporated with the magnesium ions produced by hydrothermal treatment for future application as an endosseous implant surface were investigated. Mg-incorporated Ti oxide surfaces were produced by hydrothermal treatment using Mg-containing solution on two different microstructured surfaces—abraded minimally rough or gritblasted moderately rough samples. Hydrothermal treatment produced a Mg-incorporated Ti oxide layer with nanoporous surface structures. Mg-incorporated surfaces showed surface morphologies and surface roughness values almost identical to those of untreated smooth or microrough surfaces at the micron scale. Mg incorporation increased the mRNA expressions of key osteoblast genes and integrins in cells grown on both the smooth and the microrough surfaces. These results indicate that a Mg-incorporated nanoporous to oxide surface produced by hydrothermal treatment may improve implant–bone healing by enhancing the attachment and differentiation of osteoblastic cells [33].

A variety of surface-textured implants were prepared; nonmicroroughened implants were prepared by machining Ti–6Al–4V alloy in a cylindrical form; microroughened implants were prepared by sandblasting machined implants; and

submicrofeatured implants were created by anodic oxidation of the sandblasted implants. Implants were placed into rat femurs and subjected to biomechanical, interfacial, and histological analyses at 1 and 2 weeks postimplantation. It was concluded that a submicrofeatured titanium surface created by a combination of sandblasting and anodic oxidation enhances the strength of early-stage osseointegration, primarily because of the increased resistance of periimplant bone tissue against external force rather than modulation of bone morphogenesis [34].

12.4.2 Porosity-Controlled Surface and Texturing

Void metal composite is a porous metal developed to fix a prosthesis to bone by tissue ingrowth. The material is made using techniques that produce structures with controlled porosity, density, and physical properties. The ability to produce a range of structures creates porosities to study the effects of pore size, shape, and density on bone/metal interface strength. Ti–6Al–4V is the metal of choice for the void metal composite. Structures with spherical pore size ranging from 275 to 650 μm have been fabricated with up to 80% theoretical densities. The optimum structure for attachment strength seems to be a pore size of 450 μm and 50% theoretical density [35]. The control porosity can be achieved by blasting with alumina or titania as well [36].

Petronis et al. [37] developed a model system for studying cell–surface interactions based on microfabricated cell culture substrates. Porous surfaces consisting of interconnecting channels with openings of subcellular dimensions are generated on flat, single crystal, silicon substrates. Channel size (width, depth), distribution, and surface coating can be varied independently and used for systematic investigation of how topographical, chemical, and elastic surface properties influence cell or tissue biological responses. Model porous surfaces have been produced by using two different microfabrication methods. Submicron-sized channels with very high depth-to-width aspect ratios (up to 30) have been made by using electron beam lithography and anisotropic reactive ion etching into single-crystal silicon. Another method uses thick-resist photolithography, which can be used to produce channels wider than 1 μm and with depth-to-width aspect ratios below 20 in an epoxy polymer [37]. Xiaoxiong et al. [38] created pits with controlled pit density and geometry to exhibit porosity-controlled surfaces. The pit initiation process on CpTi in bromide solution was investigated by means of surface analysis. The results showed that the titanium surface film formed by anodic polarization in bromide solution was mainly TiO_2 . Prior to the pit initiation, Br ions were absorbed and accumulated on localized spots of the TiO_2 film, forming bromine nuclei containing mostly TiBr_4 . The bromine nuclei grew into the critical nuclei when the film was in the critical state of breaking down. The depth of the critical nuclei was equal to or less than 3 nm. It was mentioned that, in the system of titanium/bromide solution, the critical surface concentration was 25–35 wt% and was independent of the temperature and concentration of the solution [38].

The *in vitro* mineralization of osteoblast-like cells on CpTi with different surface roughness was examined. CpTi disks were polished through 600 grit SiC paper

(grooved), polished through 1- μm diamond paste (smooth), or sandblasted (rough). The disks were cleaned, acid passivated, and UV sterilized (254 nm, 300 $\mu\text{W}/\text{cm}^2$). Osteoblast-like cells were harvested from rat pups and were cultured. The cultures were grown for 6 or 12 days in the media supplemented with 5 mM β -glycerophosphate. It was found that (i) *in vitro* mineralization responses were independent of surface roughness and (ii) Alizarin red staining indicated small zones of mineralization on all surfaces, indicating that surface topography is known to affect osteoblast-like cell activities [36].

Ungersboeck et al. [39] investigated five types of limited contact dynamic compression plates of CpTi with different surface treatments and electropolished stainless steel limited contact dynamic compression plates. The surface roughness parameters and chemical surface conditions were determined and checked for probable surface contamination. After an implantation period of 3 months on long sheep bones, the soft tissue adjacent to the plates was evaluated histomorphometrically. The difference in roughness parameters was statistically significant for most surface conditions. It was reported that (i) a correlation was found between the surface roughness of the implants and the thickness of the adjacent soft tissue layer, (ii) the thinnest soft tissue reaction layer with a good adhesion to the implant surface was observed for the titanium anodized plates with coarse surface (20% nitric acid at 60°C for 30 min), and (iii) smooth implants, in particular the electropolished stainless steel plates, induced statistically significant thicker soft tissue layers [39]. Larsson et al. [40] investigated the bone formation around titanium implants with varied surface properties. Machined and electropolished samples with and without thick anodically formed surface oxide were prepared and inserted in the cortical bones of rabbits (1, 3, and 6 weeks). It was found that (i) light microscopic morphology and morphometry showed that all implants were in contact with bone and had a large proportion of bone within the threads at 6 weeks, (ii) the electropolished implants, irrespective of anodic oxidation, were surrounded by less bone than the machined implants after 1 week, (iii) after 6 weeks the bone volume as well as the bone–implant contact (BIC) were lower for the merely electropolished implants than for the other three groups, and (iv) a high degree of bone contact and bone formation are achieved with titanium implants that are modified with respect to oxide thickness and surface topography; however, the result with the smooth (electropolished) implants indicates that a reduction of surface roughness, in the initial phase, decreases the rate of bone formation in rabbit cortical bone [40]. The topography of titanium implants is of importance with respect to cellular attachment. Chung and McAlarney [41] examined the topographies of three as-received implant systems (Nobelpharma, Swede-Vent, and Screw-Vent), followed by thermal (700°C for 240 min) and anodic oxidation (70 V in 1 M acetic acid solution) of the fixtures. Fixtures were self-tapped into freshly sacrificed swine rib bone. It was found that (i) thermal and anodic oxidation as well as implantation shear stress had no effect on topography and (ii) the growth of oxides and implantation shear stress had no effect on topography [41].

Thelen et al. [42] investigated mechanics issues related to potential use of a recently developed porous titanium material for load-bearing implants. This

material may have advantages over solid Ti for enhancing the bone–implant interface strength by promoting bone and soft tissue ingrowth, and for reducing the bone–implant modulus mismatch, which can lead to stress shielding. It was mentioned that (i) simple analytic models provide good estimates of the elastic properties of the porous Ti and (ii) the moduli can be significantly reduced to decrease the mismatch between solid Ti and bone, achieving the mechanical compatibility proposed by Oshida [43]. The finite element simulations show that bone ingrowth will dramatically reduce stress concentrations around the pores [42]. Takemoto et al. [44] prepared porous bioactive titanium implants (porosity of 40%) by a plasma spray method and subsequent chemical and thermal treatments of immersion in a 5 M aqueous NaOH solution at 60°C for 24 h, immersion in distilled water at 40°C for 48 h, and heating to 600°C for 1 h. It was reported that compression strength and bending strength were 280 MPa (0.2% offset yield strength 85.2 MPa) and 101 MPa, respectively. For *in vivo* analysis, bioactive and nontreated porous titanium cylinders were implanted into 6 mm diameter holes in rabbit femoral condyles. It was found that (i) the percentage of BIC of the bioactive implants was significantly larger than for the nontreated implants at all postimplantation times (13.5/10.5, 16.7/12.7, 17.7/10.2, 19.1/7.8 at 2, 4, 8, and 16 weeks, respectively) and (ii) the percentage of bone area ingrowth showed a significant increase with the bioactive implants, whereas with the nontreated implants it appeared to decrease after 4 weeks (10.7/9.9, 12.3/13.1, 15.2/9.8, 20.6/8.7 at 2, 4, 8, and 16 weeks, respectively), suggesting that porous bioactive titanium has sufficient mechanical properties and biocompatibility for clinical use under load-bearing conditions [44].

12.4.3 Mechanical Property and Its Effect

The high cycle fatigue strength of porous-coated Ti–6Al–4V is approximately 75% less than the fatigue strength of uncoated Ti–6Al–4V. Kohn et al. [45] designed their study to separate the effects of three parameters thought to be responsible for this reduction: interfacial geometry, microstructure, and surface alterations caused by sintering. To achieve the goal of one parameter variation, hydrogen-alloying treatments, which refined the lamellar microstructure of β -annealed and porous-coated Ti–6Al–4V, were formulated. It was found that (i) Ti–6Al–4V subjected to hydrogen-alloying treatment was 643–669 MPa, which was significantly greater than the fatigue strength of β -annealed Ti–6Al–4V (497 MPa) and also greater than the fatigue strength of preannealed, equiaxed Ti–6Al–4V (590 MPa); however, (ii) the fatigue strength of porous-coated Ti–6Al–4V is independent of microstructure. It is, therefore, concluded that the notch effect of the surface porosity does not allow the material to take advantage of the superior fatigue crack initiation resistance of a refined α -grain size [45].

Open-cell porous Ti with a porosity ranging from 35% to 84% was successfully manufactured by sintering titanium fibers. The microstructure of the porous titanium was observed by scanning electron microscopy (SEM) and the compressive mechanical properties were tested. By adjusting the spiral structure of the porous

titanium, the pore size can be controlled in a range of 150–600 μm . With the increasing of the porosity, compressive yield strength and modulus decrease as predicated. However, high mechanical properties were still obtained at a medium porosity, for example, the compressive yield strength and the modulus are as high as 100–200 MPa and 3.5–4.2 GPa, respectively, when the porosity is in the range of 50–70%. It was suggested that the porous titanium is strong enough to resist handling during implantation and *in vivo* loading. It is expected to be used as bio-compatible implant because their interconnected porous structures permit bone tissue ingrowth and body fluid transportation [46].

Porous Ti–6Al–4V alloy was fabricated using the EBM process. The phases of the as-received powder and fabricated samples were characterized using X-ray diffraction (XRD) analysis. The XRD peaks of both diffraction patterns agree well, which indicated that the EBM process has not changed the composition of Ti–6Al–4V. The fabricated samples exhibited a Vickers microhardness value of around 428 HV. The compression and three-point bending tests were performed to evaluate the mechanical properties of the porous Ti–6Al–4V implant with a porosity of around 60%. The compressive yield strength, Young's modulus, and ultimate compressive strength were 194.6 MPa, 4.25 GPa, and 222.6 MPa, respectively. The bending stiffness and bending strength were 3.7 GPa and 126.3 MPa, respectively. These results demonstrated that the porous Ti–6Al–4V implant with a low stiffness and high porosity could be a promising biomaterial for biomedical applications [47].

Metallic biomaterials are widely used to restore the lost structure and functions of human bone. Due to the large number of joint replacements, there is a growing demand for new and improved orthopedic implants. More specifically, there is a need for novel load-bearing metallic implants with low effective modulus matching that of bone in order to reduce stress shielding and consequently increase the *in vivo* lifespan of the implant. The effective modulus of Ti–6Al–4V alloy structures has been tailored between 7 and 60 GPa and porous Ti alloy structures containing 23–32 vol% porosity showed modulus equivalent to human cortical bone. *In vivo* behavior of porous Ti–6Al–4V alloy samples in male Sprague–Dawley rats for 16 weeks demonstrated a significant increase in calcium within the implants, indicating excellent biological tissue ingrowth through interconnected porosity. *In vivo* results also showed that total amount of porosity plays an important role in tissue ingrowth [48].

12.4.4 Foam Metal

A foam metal is a cellular structure consisting of a solid metal, frequently aluminum, containing a large volume fraction of gas-filled pores. The pores can be sealed (closed-cell foam), or they can form an interconnected network (open-cell foam). The defining characteristic of metal foams is a very high porosity: typically 75–95% of the volume consists of void spaces. The strength of foamed metal possesses a power law relationship to its density; that is, a 20% dense material is more than twice as strong as a 10% dense material. The foam-shaped materials

exhibit a continuously connected ligamented, reticulated open-cell geometry having a duodecahedral cell shape. The foam-shaped material is in a density ranging from 1% to 20% theoretical and a cell density of 10–50 cells per linear inch, with material density and cell density independently variable. Foamed materials are presently produced in a wide range of plastics, metals, and composites having either solid or tubular ligaments. The metals include aluminum, nickel, copper, silver, zinc, leads, tin, magnesium, and stainless steel [49]. Metallic foams typically retain some physical properties of their base material. Foam made from nonflammable metal will remain nonflammable and the foam is generally recyclable back to its base material. Coefficient of thermal expansion will also remain similar while thermal conductivity will likely be reduced [49].

Open-celled metal foams are usually replicas using open-celled polyurethane foams as a skeleton and have a wide variety of applications including heat exchangers (compact electronics cooling, cryogen tanks, PCM heat exchangers), energy absorption, flow diffusion, and lightweight optics [50–52]. Closed-cell metal foams are commonly made by injecting a gas or mixing a foaming agent (frequently TiH_2) into molten metal [53]. In order to stabilize the molten metal bubbles, high-temperature foaming agents (nano- or micrometer-sized solid particles) are required. The size of the pores, or cells, is usually 1–8 mm. Closed-cell metal foams are primarily used as an impact-absorbing material, similarly to the polymer foams in a bicycle helmet but for higher impact loads.

Surface modifications of dental and medical implants are very important for various reasons. As numerous reports indicate, the surface texture should be preferably rough for enhanced mechanical retention between the implant surface and newly grown bone structure. Moreover, increased porosity in the modified surface layer will show lower mechanical properties than the bulk material, and their values are close to those of the implant-receiving soft/hard vital tissues. This is the so-called mechanical compatibility. Besides this and biological compatibility, there is the third compatibility, which was proposed by the present author and is called morphological compatibility [54]. Titanium alloy is also used for medical implants and is well thought of in that role. However, it seems that the miracle metal, for example, as strong as steel but half the weight—is inconveniently stiff. The human bone that it replaces is bendier, and superstiff titanium replacements can cause adjacent bones, relieved of loads which would normally be put on them due to their yielding neighbors, to atrophy from lack of work. Also a normal titanium implant, though it often bonds well with the bone it is attached to, can break free. Recently, foamed titanium was developed—called “foamalloxy endoskeletons,” claiming that the mechanical properties of titanium foams made this way closely approach those of the human bone [55], (<http://www.news.com.au/technology/doctors-discover-how-to-make-titanium-bones/story-e6frfro0-1225928889483#ixzz24bb7N5E3>). Zimmer introduces the first porous metal interbody implant for lumbar spine (http://www.redorbit.com/news/health/1112646068/zimmer_introduces_first_porous_metal_interbody_implant_for_lumbar_spine/). Titanium foams produced via the space-holder method are used for spinal fusion devices since their combination of an open-cell structure and bone-like mechanical properties promises potentially excellent bone

ingrowth. Earlier studies have indicated that the size of the pores and interconnects must be greater than 100 μm for effective bone ingrowth and vascularization. Hence, the quantification of the pore and interconnect size is required for efficient scaffold design. μCT was used to obtain the 3D structure of Ti foams with three levels of porosity (51%, 65%, and 78%). Novel algorithms were then applied to quantify both the pore and interconnect size of Ti foams as a function of porosity. All foams possessed a modal pore and interconnect size in excess of 300 μm , satisfying the requirement of being greater than 100 μm . The pore and interconnect size also dominates the flow properties or permeability of open-cell structures. Therefore, the μCT data was also used to generate a mesh for computational fluid dynamics analysis to predict the permeability. The calculated permeability ($117\text{--}163 \times 10^{-12} \text{ m}^2$ depending on direction) for the Ti foams with 65% porosity was first validated against experimental measurements ($98\text{--}163 \times 10^{-12} \text{ m}^2$) and then compared to prior authors' measurements in healthy cancellous bovine bone ($233\text{--}465 \times 10^{-12} \text{ m}^2$). The close match among all the permeability values proves the suitability of the material for biomedical skeletal-implant applications [56].

A novel route for producing a new class of titanium foams for use in biomedical implant applications was introduced. These foams are hierarchically porous, with both the traditional large ($> 300 \mu\text{m}$) highly interconnected pores and, uniquely, wall struts also containing micron-scale ($0.5\text{--}5 \mu\text{m}$) interconnected porosities. The fabrication method consists of first producing a porous oxide precursor via a gel casting method, followed by electrochemical reduction to produce a metallic foam. The method offers the unique ability to tailor the porosity at several scales independently, unlike traditional space-holder techniques. Reducing the pressure during foam setting increased the macropore size. The intrastrut pore size can be controlled independently of macropore size by altering the ceramic loading and sintering temperature during precursor production. Typical properties for an 80% porous Ti foam were elastic modulus of $\sim 1 \text{ GPa}$, a yield strength of 8 MPa, and a permeability of 350 Darcies, all of which are in the range required for biomedical implant applications [57].

12.5 Near-Net Shape Forming

12.5.1 Net Shape Forming

Net shape processing refers to any manufacturing process that creates an object in its finished form *without* the need for finish machining or other actions. The obvious benefit is in the saved labor needed for finishing and the consequent cost savings. Less obvious is the potential for quicker production, which better fits the overall lean production paradigm. Net shape processes are as familiar as the forming of glass bottles or the injection molding of simple plastics. Preparation of new materials and net shape forming technologies are recognized as the worldwide research frontier. The research directions in the field include: (1) synthesis, processing, and forming technologies of nanometric materials, high-temperature materials

by combustion synthesis, and composites, (2) improvement of the accuracy of traditional material processing technologies such as casting, forging, and welding, and (3) surface engineering of materials. Research work in this field has the characteristics of integration of fundamental research and applied research, and industrialization of high-technology.

12.5.2 Net Shape Nanostructured

The plasma spray technique has been used by several researchers to deposit nanostructured ceramic coatings, but there is no available literature discussing how to fabricate a bulk, freestanding nanostructured component by such a technique. Net shape nanostructured Al_2O_3 structures have been fabricated using the plasma spray technique. Plasma spray parameters were controlled with a proprietary cooling technique to retain a large fraction of nanosize Al_2O_3 powder particles in the spray deposit. Partially melted nanosize Al_2O_3 particles were trapped between the fully melted coarser, micrometer size Al_2O_3 grains. It was found that densification of the spray deposit has been dominated by both solidification and solid-state sintering. It was suggested that a variety of nanostructured materials and their combinations can be fabricated to NNSs by espousing a similar processing approach. The plasma spray technique is one such method that has been used by several researchers to deposit nanostructured coatings such as WC, Cr_3C_2 , $\text{Al}_2\text{O}_3\text{--TiO}_2$ [58].

The importance of the stochastic nature of forging operations, especially for net-shape accuracy, has been widely recognized. However, it is an under-researched area in terms of effective methods and computational tools for easy industrial implementation and applications. Monte Carlo simulation, response surface method, and most probable point analysis are used to quantify probabilistic characteristics of the shape and dimensional errors in net-shape metal forming processes. A two-step optimization approach is developed to minimize systematic errors using a direct compensation method for die shape modification and to reduce random variations through a control-variable method. Two industrial-based case studies, that is, forging of a 2D aerofoil component and forward extrusion of a cylinder, were conducted with good results obtained for much improved accuracy. It was reported that the approach can be easily applied to general metal forming processes for both 2D and 3D cases where achievable accuracy is an essential criterion [59].

12.5.3 Near-Net Shape Technology

Near-net shape (NNS) is an industrial manufacturing technique. The name implies that the initial production of the item is very close to the final (net) shape, reducing the need for surface finishing. Reducing traditional finishing such as machining or grinding eliminates more than two-thirds of the production costs in some industries. Forging is the process of beating metal by compressing it and making it flow into the desired shape of tool or die geometry. The term *near-net shape* implies that the die so produced is as close to the final product as possible, leading to marginal

machining allowances and greater accuracy. Forming process design via finite element simulation is the state of the art. Advantages of NNS forging can include (1) increased strength due to cold work and better grain flow, (2) reduction in energy cost, (3) no wastages of material, (4) excellent surface finish and improved corrosion and wear resistance, and (5) higher productivity and reduced machining.

Recently, vacuum plasma spray forming (VPSF) has been identified as a process capable of manufacturing NNS components for advanced technology applications such as the aerospace, defense, and chemical process industries. By optimizing the deposit structure via intelligent control of process parameters and utilizing postdeposition heat treatments, deposit structures with properties better than conventionally cast materials and, in some cases, equivalent to wrought materials can be produced. In the current study, one of the most important and widely used titanium alloys, Ti–6Al–4V, was chosen to form a NNS structure by VPSF process. The microstructure and properties of the initial powder and the as-deposited component were characterized. It was found that the as-deposited material consisted of approximately 90% martensite present in the form of fine lathes (~ 500 nm in width), surrounded by a residual β phase. The as-sprayed material failed at low elongations ($\sim 1\%$) when tested in tension. It was reported that (i) the level of porosity in the heat-treated materials was reduced to as low as 1% and the ductility were markedly improved ($\sim 10\%$) by all heat treatments and (ii) the elastic modulus of the heat-treated structures was improved (115–120 GPa) significantly and was close to those of wrought heat-treated materials [60].

NNS is an innovative concept in industrial manufacturing. The main focus of this technology is to produce parts as near as possible to their final shape and contour by implementing nonchipping techniques. In this way, the manufacturing gives the possibility of a finished product with minimal cutting. NNS technology also generates the opportunity to reduce the productive steps for a given process chain. Both the above-mentioned characteristics have the same main goal: achieving cost reduction. This fundamental target incorporates several other advantages, such as reduction of process variability, quality improvement in the finished product, and the possibility to focus the design of mechanical devices on functional features, eliminating technical constraints imposed by the process. It was evaluated whether it is more convenient to produce the part by implementing a traditional production chain or an innovative one, based on NNS techniques. The first step was to locate the available technologies in order to produce the selected part. There are two alternatives: a traditional cutting manufacture, performed with a numerical control turning machine, and a NNS technique, characterized only by deformation processes. The next step was to detect the main differential costs between the two opportunities. Comparing technical data and information available in literature, the main differential voices of cost (raw material, amortization, manpower, and direct setup) were detected [61].

In order to achieve the better condition for fit, for example, superstructure for implants or denture base for prostheses, the accuracy of the final products are very crucial and need to be improved. Among various manufacturing technologies, NNS

forming and nanotechnology are most promising and supportive for these specific aims. New classes of fabrication processes, such as direct-write technique [62] and solid freedom fabrication [63], have established the capability to produce 3D parts faster, cheaper, and with added functionality. The choice of starting materials and the specific processing technique will produce unique microstructures that impact the final performance, especially of macroscopic structural and electronic parts. Furthermore, the ability to do pointwise deposition of one or more materials provides the opportunity for fabricating structures with novel micro- and macro-structural features, such as microengineered porosity, graded interfaces, and complex multimaterial constructions. NNS processing offers cost reduction by minimizing machining, reducing part count, and avoiding part distortion from welding. NSS technologies such as flow-forming (FF), casting, forging, powder metallurgy (P/M) methods, 3D laser deposition, and plasma arc deposition have been explored for potential use in tubular geometries and other shapes of varying complexity. It appears that the reduction in cost of a given titanium product will be maximized by achieving improvements in all of the manufacturing steps, from extraction to finishing [64].

12.6 Nanotechnology—Materials and Structures

One major determination of the suitability of various engineering materials for use in biological settings is the relative strength of adhesion obtained between those materials and their contacting viable phases. Maximal adhesive strength and immobility are desired for orthopedic and dental implants. For example, while minimal bioadhesion is critical to preventing unwanted thrombus formation in cardiovascular devices, plaque buildup on dental prostheses and bacterial fouling [65]. Attention should be directed to adhesive phenomena in the oral environment, examining new surface conditioning methods for the prevention of microorganism deposits as well as the promotion of excellent tissue bonding to implanted prosthetic devices. Other bioadhesive phenomena considered included those important to the safe and effective function of new cardiovascular devices. Historically, ceramic biomaterials, such as alumina and zirconia, were anticipated to function as an inert material in the body. Nowadays, the emphasis is more on applying these materials to create a bioactive scaffold that stimulates the construction of a well-functioning bone–implant interface [66–70]. It is often stated that a specific combination of micro- and nanotopography is required to stimulate osseointegration or to cause mechanisms like mechanical anchoring of the implant in the body, stimulating cells to produce a higher density of focal adhesions [71–73], or even presenting an antibacterial effect [74].

The requirements imposed by the enormous scale and overall complexity of designing new implants or complete organ regeneration are well beyond the reach of present technology in many dimensions, including nanoscale, as researchers do not yet have the basic knowledge required to achieve these goals. The need for a

synthetic implant to address multiple physical and biological factors imposes tremendous constraints on the choice of suitable materials. There is a strong belief that nanoscale materials will produce a new generation of implant materials with high efficiency, low cost, and high volume. The nanoscale in materials processing is truly a new frontier. Metallic dental implants have been used successfully for decades, but they have serious shortcomings related to their osseointegration and the fact that their mechanical properties do not match those of bone—poor mechanical compatibility, as the present author pointed many places in this book [75]. The role of nanostructured titanium surfaces in a number of aspects of *in vivo* bone—implant integration, and, in particular, their potential advantages over microstructured titanium surfaces as well as their specific contribution to osteoconductivity are largely unknown [76].

12.6.1 Nanostructured Hydroxyapatite

There are studies on nanostructured hydroxyapatite [77–80], and the common finding was that nanoparticle hydroxyapatite coating films enhanced osseointegration of Ti implants, and hence possesses high potential for the orthopedic and dental applications. The osseointegration was evaluated in rabbit cancellous bone of titanium implants with a microtopographically complex surface structure produced by gritblasting/acid etching with or without the addition of surface calcium ion chemistry. Microstructured titanium implants were hydrothermally treated in an alkaline Ca-containing solution to produce a nanostructured Ca-incorporated oxide surface layer. Twenty implants (10 control and 10 experimental) were placed in the femoral condyles of 10 New Zealand White rabbits. Histomorphometric analysis was performed 6 weeks after implantation. It was found that (i) Ca-incorporated and untreated control implants showed similar surface morphologies and surface roughness values at the micron scale, (ii) untreated microstructured Ti implants achieved a high degree of BIC, and Ca incorporation further increased BIC%, and (iii) active new bone apposition was found on surfaces of Ca-incorporated implants in areas of loose trabeculae. It was then concluded that the nanostructured Ca-incorporated oxide surface significantly enhanced osteoconductivity of microstructured Ti implants in rabbit cancellous bone, indicating that the surface produced by simple hydrothermal treatment may be effective in improving the osseointegration of implants with microtopographically complex surface structures in areas of loose cancellous bone [81].

Nano- and microphase HA film was formed on a TiO₂ nanonetwork surface by simple electrochemical treatment. The range of lateral pore size of the network specimen was about 10–120 nm on Ti surface anodized in 5 M NaOH solution at 0.3 A for 10 min. Nanonetwork TiO₂ surfaces were formed by this anodization step, which acted as templates and anchorage for growth of the HA during subsequent pulsed electrochemical deposition process at 85°C. The nanoneedle-like precipitates formed under low SBF concentration were identified to be HA crystals orientated parallel to the *c*-axis direction. It was found that, with increasing

electrolyte concentration, needle-like deposits transferred to the plate-like and microplate-like precipitates in the case of high SBF concentration [82].

12.6.2 Nanostructured Titanium

Nanostructured titanium-based biomaterials with tailored porosity are important for cell adhesion, viability, differentiation, and growth. Newer technologies like foaming or low-density core processing were recently used for the surface modification of titanium alloy implant bodies to simulate bone ingrowth and improve osseointegration and cell adhesion, which in turn play a key role in the acceptance of the implants [83].

Bacterial infection of in-dwelling medical devices is a growing problem that cannot be treated by traditional antibiotics due to the increasing prevalence of antimicrobial resistance and biofilm formation. Bacterial adhesion can be prevented through nanosurface modifications of the medical device alone, due to changes in surface parameters. Accordingly, titanium was created to possess nanotubular surface topographies of highly controlled diameters of 20, 40, 60, or 80 nm, sometimes followed by heat treatment to control chemistry and crystallinity, through a novel anodization process. It was found that through the control of Ti surface parameters including chemistry, crystallinity, nanotube size, and hydrophilicity significantly changed responses of both *Staphylococcus epidermidis* and *Staphylococcus aureus* (pathogens relevant for orthopedic and other medical device related infections) were measured. Specifically, heat treatment of 80-nm diameter titanium tubes produced the most robust antimicrobial effect of all surface treatment parameters tested, indicating that surface properties of nanostructured titanium improve tissue growth (as has been previously observed with nanotubular titanium), while simultaneously reducing infection without the use of pharmaceutical drugs [84].

A major problem with transcutaneous osseointegrated implants is infection, mainly due to improper closure of the implant–skin interface. Therefore, the design of transcutaneous osseointegrated devices that better promote skin growth around these exit sites needs to be examined and, if successful, would clearly limit infection. Due to the success already demonstrated for orthopedic implants, developing surfaces with biologically inspired nanometer features is a design criterion that needs to be investigated for transcutaneous devices. Based on this background, the influence of nanotextured titanium (Ti) created through electron beam evaporation and anodization on keratinocyte (skin-forming cell) function was investigated. Electron beam evaporation created Ti surfaces with nanometer features while anodization created Ti surfaces with nanotubes. Conventional Ti surfaces were largely micron rough, with few nanometer surface features. Results revealed increased keratinocyte adhesion in addition to increased keratinocyte spreading and differences in keratinocyte filopodia extension on the nanotextured Ti surfaces prepared by either electron beam evaporation or anodization compared to their conventional, unmodified counterparts after 4 h. Results further revealed increased keratinocyte proliferation and cell spreading over 3 and 5 days only on the nanorough Ti surfaces

prepared by electron beam evaporation compared to both the anodized nanotubular and unmodified Ti surfaces. It was concluded that the *in vitro* study provided the first evidence that nanomodification techniques should be further researched as a means to possibly improve skin growth, thereby improving transcutaneous osseointegrated orthopedic implant longevity [85].

There are numerous articles on fabrication methods for titanium and titania nanotube structures [86–94]. The most common fabrication method for nanotube structures is an anodically electrochemical treatment in phosphoric acid solutions; for example, Feng et al. [93] used 1 M $(\text{NH}_4)_2\text{SO}_4$ containing 0.25 M NH_4F and Sul [94] employed 1 M H_3PO_4 plus 0.4 wt% HF. Unique work was reported by Xin et al. [95], developing of strontium-releasing implants capable of stimulating bone formation and inhibiting bone resorption for curing osteoporosis. Well-ordered SrTiO_3 nanotube arrays capable of Sr release at a slow rate and for a long time were successfully fabricated on titanium by simple hydrothermal treatment of anodized titania nanotubes. The, thus, fabricated surface architecture combined the functions of nanoscaled topography and Sr release to enhance osseointegration while at the same time leaving space for loading of other functional substances. The *in vitro* experiments reveal that the SrTiO_3 nanotube arrays possess good biocompatibility and can induce precipitation of hydroxyapatite from SBFs. Ti-based implant with SrTiO_3 nanotube arrays is an ideal candidate for osteoporotic bone implants. The proposed method can also be extended to load other biologically useful elements such as Mg and Zn [95]. Moreover, characterization studies on thus obtained titanium and titania nanotubes were conducted [96–100]. It is well known that the growth of osteoblast cultured on titanium with nanotube layers can be significantly increased compared to unanodized surfaces. The corrosion behavior of titanium with nanotube layers was studied in naturally aerated Hank's solution using open circuit potentials (OCP), electrochemical impedance spectroscopy (EIS) and potentiodynamic polarization tests. The electrochemical results indicated that TiO_2 nanotube layers on titanium showed a better corrosion resistance in simulated biofluid than that of smooth Ti. The OCP, corrosion rate (I_{corr}), passive current density (I_{pass}), and oxygen evolution potential (E_o) were significantly influenced by titanium oxide-nanotube layers acquired by anodization. It was reported that (i) the anatase nanotube layer showed higher OCP and smaller current density than the amorphous nanotube layer, (ii) EIS analysis showed that the annealing had a significant effect on the corrosion resistance of the outer tube layer (R_t) but little effect on the corrosion resistance of the interbarrier layer (R_b) for nanotube layers, and (iii) titanium with TiO_2 nanotube layers has an adequate electrochemical behavior for use as a dental implant material [95]. Nanosized surface topography on an implant material has the capability of stimulating the acceptance of the material in its host surrounding. Fine tuning of nanotopography feature size has been shown to trigger differentiation of mesenchymal stem cells into bone cells *in vitro*. For this purpose, we have created well-defined nanosized titania dot- and pillar-like structures on mechanically polished Ti substrates using a through-mask anodization technique with an anodic porous alumina template. The anodization technique allowed the titania structure dimensions to be precisely tuned in the range

15–140 nm in a single electrolyte system. The fabricated surfaces serve as good model surfaces for precise studies of *in vitro* cell behavior. The through-mask anodization technique was used directly on bulk Ti surfaces, thus demonstrating a potential application for patterning of actual Ti implant surfaces [97].

12.6.3 Nanostructured Titania

Macak et al. [101] reported on the fabrication of self-organized porous oxide-nanotube layers on the biomedical titanium alloys Ti–6Al–7Nb and Ti–6Al–4V by a simple electrochemical treatment. These two-phase alloys were anodized in 1 M $(\text{NH}_4)_2\text{SO}_4$ electrolytes containing 0.5 wt% of NH_4F . It was shown that (i) under specific anodization conditions, self-organized porous oxide structures can be grown on the alloy surface, (ii) SEM images revealed that the porous layers consist of arrays of single nanotubes with a diameter of 100 nm and a spacing of 150 nm, (iii) for the V-containing alloy, enhanced etching of the β -phase is observed, leading to selective dissolution and an inhomogeneous pore formation, and (iv) for the Nb-containing alloy, an almost ideal coverage of both phases is obtained. According to XPS measurements, the tubes are a mixed oxide with an almost stoichiometric oxide composition and can be grown to thicknesses of several hundreds of nanometers, suggesting that a simple surface treatment for Ti alloys has high potential for biomedical applications [101]. A vertically aligned nanotube array of titanium oxide was fabricated on the surface of titanium substrate by anodization. The nanotubes were then treated with NaOH solution to make them bioactive and to induce growth of hydroxyapatite (bone-like calcium phosphate) in a SBF. It is found that (i) the presence of TiO_2 nanotubes induces the growth of a “nanoinspired nanostructure”, that is, extremely fine-scale (~ 8 nm feature) nanofibers of bioactive sodium titanate structure on the top edge of the ~ 15 nm thick nanotube wall, (ii) during the subsequent *in vitro* immersion in a SBF, the nanoscale sodium titanate, in turn, induced the nucleation and growth nanodimensioned hydroxyapatite phase, and (iii) such TiO_2 nanotube arrays and associated nanostructures can be useful as a well-adhered bioactive surface layer on Ti implant metals for orthopedic and dental implants as well as for photocatalysts and other sensor applications [102].

Three types of bioactive polymethylmethacrylate (PMMA)-based bone cement containing nanosized titania (TiO_2) particles were prepared, and their mechanical properties and osteoconductivity are evaluated by Goto et al. [103]. The three types of bioactive bone cement were un50 wt% silanized TiO_2 , 50 wt% silanized TiO_2 , and 60 wt% mixed to PMMA. Commercially available PMMA cement was used as a control. The cements were inserted into rat tibiae and allowed to solidify *in situ*. After 6 and 12 weeks, tibiae were removed for evaluation of osteoconductivity. It was reported that (i) bone cements using silanized TiO_2 were directly apposed to bone, while unsilanized TiO_2 cement and PMMA control were not, (ii) the osteoconduction of cement with 60 wt% of silanized TiO_2 was significantly better than that of the other cements at each time interval, and (iii) the compressive strength of cement with 60 wt% of silanized TiO_2 was equivalent to that of PMMA, indicating

that cement with 60 wt% of TiO_2 was a promising material for use as a bone substitute [103]. Since it is essential for the gap between the hydroxyapatite-coated titanium and juxtaposed bone to be filled out with regenerated bone, promoting the functions of bone-forming cells is desired. In order to improve orthopedic implant performance, Sato et al. [104] synthesized nanocrystalline hydroxyapatite (HA) powders to coat titanium through a wet chemical process. The precipitated powders were either sintered at 1100°C for 1 h in order to produce microcrystalline size HA or were treated hydrothermally at 200°C for 20 h to produce nanocrystalline HA. These powders were then deposited onto titanium by a room temperature process. It was reported that (i) the chemical and physical properties of the original HA powders were retained when coated on titanium by the room temperature process, (ii) osteoblast adhesion increased on the nanocrystalline HA coatings compared to traditionally used plasma-sprayed HA coatings, and (iii) greater amounts of calcium deposition by osteoblasts cultured on Y-doped nanocrystalline HA coatings were observed [104].

In order to improve human cell growth on titanium (Ti) used for dental implants, formation of a nanonetwork surface oxide layer created by an electrochemical anodization treatment was examined. An electrochemical anodization treatment was used to produce a network oxide layer on Ti surface. Surface characterization of the network layer was carried out using thin film X-ray diffractometer and field emission SEM. Human bone marrow mesenchymal stem cells (hMSCs) were made to express green fluorescent protein (GFP) by retroviral transduction. The GFP signal was measured *in situ* to assess *in vitro* and *in vivo* cell growth on Ti surfaces. The *in vivo* experiments on Ti-supported cell growth were carried out on the back skin of nude mice. Alizarin red staining and immunofluorescent staining were used to observe cell differentiation. A multilayer TiO_2 nanonetwork was produced rapidly on Ti surface using a simple electrochemical anodization treatment. It was found that (i) the TiO_2 nanonetwork layer on the anodized Ti surfaces significantly improved *in vitro* and *in vivo* hMSC growth, as assessed by measurement of GFP fluorescence, relative to hMSC growth on untreated Ti surfaces, (ii) the TiO_2 nanonetwork layer on the anodized Ti surfaces can also induce the differentiation of hMSCs after a 28-day *in vivo* test, and (iii) the formation of TiO_2 nanonetwork on the Ti surfaces can increase the hMSC growth *in vitro* and *in vivo* [98]. Nanostructures have pronounced effects on biological processes such as growth of cells and their functionality. Advances in biomaterial surface structure and design have resulted in improved TE. Nanotechnology can be utilized for optimization of titanium implants with a formation of vertically aligned TiO_2 nanotube arrays on the implant surface. The anodic oxidation of the titanium implant surface to form a TiO_2 nanotube array involves electrochemical processes and self assembly. Brammer et al. [99] discussed the mechanism of nanotube formation, nanotube biocharacteristics, and their emerging role in soft and hard TE as well as in regenerative medicine and the beneficial effects of surface nanotubes on cell adhesion, proliferation, and functionality in relation to potential orthopedics applications [99].

Titanium and its alloys are widely used as a dental implant material in clinical dentistry and as an orthopedic implant material. A nanotubular oxide surface and

layer formed on Ti–35Ta– x Zr alloys were prepared for biomaterials. The alloy was prepared by arc melting and heat treated for 24 h at 1000°C in argon atmosphere and then water quenched. Ti oxide nanotubes were formed on the alloy by anodizing in H₃PO₄ containing 0.8 wt% NaF solution at 25°C. Anodization was carried out using a scanning potentiostat. Crystallization treatment of nanotube surface was carried out for 3 h at 450°C. It was observed that nanotubular oxide surface and layers consisting of highly ordered nanotubes with a wide range of diameters (ca. 150–200 μ m) and lengths (ca. 4–10 μ m) can be formed. As Zr content increased from 3% to 15%, the length of step between the bamboo knob-like columns had increasing values from approximately 50 to 140 nm. It was further reported that the nanotubes formed on the Ti–35Ta– x Zr alloy surface were amorphous structures before heat treatment, but the oxide surface had mainly the anatase structure after heat treatment [105].

There is a great demand for dental implant surfaces to accelerate the process of periimplant bone generation to reduce its healing time and enable early loading. To this end, an inverse correlation between the proliferation and functional maturation (differentiation) in osteoblasts presents a challenge for the rapid generation of greater amounts of bone. For instance, osteoblasts exhibit faster differentiation but slower proliferation on microroughed titanium surfaces. Using a unique microhierarchal topography of TiO₂ that mimics biomineralized matrices, Hori et al. [100] demonstrates that this challenge can be overcome without the use of biological agents. CpTi (grade II) disks were prepared by machining (smooth surface). To create a microtexture with peaks and valleys (micropit surface), titanium disks were acid etched. For forming 200-nm nanonodules within the micropits (nanonodules-in-micropit surface), TiO₂ was sputter deposited onto the acid-etched surface. Rat bone marrow–derived osteoblasts and NIH3T3 fibroblasts were cultured on machined smooth, micropit, and nanonodule-in-micropit surfaces. It was found that, despite the substantially increased surface roughness, the addition of 200-nm nanonodules to micropits increased osteoblast proliferation while enhancing their functional differentiation. Contrarily, this nanonodule-in-micropit surface decreased proliferation and function in fibroblasts. It was, hence, suggested that (i) the establishment of cell-selectively functionalized nano-in-micro smart titanium surfaces involve a regulatory effect on osteoblast proliferation, abrogating the inhibitory mechanism on the micropitted surface, while enhancing their functional differentiation, (ii) the biomimetic and controllable nature of this nanonodule-in-micropits surface may offer a novel micro-to-nanoscale hierarchical platform to biologically optimize nanofeatures of biomaterials, and (iii) particularly, this micro–nanohybrid surface may be an effective approach to improve current implant surfaces for accelerated bone integration [100].

12.6.4 Tissue Engineering

An interesting cell response to novel nanostructures formed on a titanium surface by a simple nonlithographic bottom-up method was reported [106]. The surface topography of bioimplant materials dramatically influences their cell response.

A set of unique structures ranging from mesoporous nanoscaffolds, nanoflowers, nanoneedles, nanorods, and octahedral bipyramids was fabricated by systematically tuning the hydrothermal conditions such as reaction medium composition, concentration, temperature, and time duration. The cytotoxicity of surface-modified Ti was assessed using human primary osteoblastic cells, and more than 90% of the cells were found to be viable after 24 h of incubation. Protein adsorption studies revealed that the surface-modified nanostructures on titanium adsorbed more proteins suggesting that they are capable of promoting cell adhesion/attachment. Immunofluorescence studies with vinculin antibody identified a distinctly different spread pattern of osteoblastic cells on hydrothermally modified nanostructured surfaces, indicating the formation of the focal adhesion points required for intracellular signaling. Based on these results, it was suggested that this study may present one of the best designs and systematic syntheses of biocompatible nanostructures on metallic Ti for orthopedic implant applications [106]. There are still unique scaffold systems developed, such as the collagen-carbon nanotubes composite matrices [107], chitosan-based hyaluronan hybrid polymer fibers system [108], bioactive porous CaSiO_3 scaffold structure [109], or a 3D porous scaffold composed of biodegradable polyesters [110].

Taylor [111] pointed out that nanotechnology offers the key to faster and remote diagnostic techniques—including new high-throughput diagnostics, multiparameter, tunable diagnostic techniques, and biochips for a variety of assays. It also enables the development of tissue-engineered medical products and artificial organs, such as heart valves, veins and arteries, liver, and skin. These can be grown from the individual's own tissues as stem cells on a 3D scaffold, 3D tissue-engineering extracellular matrix, or the expansion of other cell types on a suitable substrate. The applications that seem likely to be most immediately in place are external tissue grafts; dental and bone replacements; protein and gene analysis; internal tissue implants; and nanotechnology applications within *in vivo* testing devices and various other medical devices. Nanotechnology is applied in a variety of ways across this wide range of products. Artificial organs will demand nanoengineering to affect the chemical functionality presented at a membrane or artificial surface, and thus avoid rejection by the host. There has been much speculation and publicity about more futuristic developments such as nanorobot therapeutics, but these do not seem likely within our time horizon [111].

It is indispensable here to mention the minimally invasive dentistry (MID) and minimally invasive surgery (MIS). The MIS concept has been created to allow new thinking and a new approach to dentistry where restoration of a tooth becomes the last treatment decision rather than first consideration as at present. It provides a practical approach to caries preventive measures based on the notion of demineralization and remineralization in a microphase in order to retain healthy teeth. The medical model of MID is characterized by (1) reduction in cariogenic bacteria, (2) preventive measures, (3) remineralization of early enamel lesions, (4) minimum surgical intervention of cavitated lesions, and (5) repair of defective restorations [112]. At the same time, it is mentioned that MIS has several advantages: (1) since the surgical area is narrower, damage on surrounding soft tissue can be minimized,

(2) postoperation pain can be minimized, (3) hospital time can be shortened, and (4) early rehabilitation can be initiated [113]. These MIS in both dentistry and medicine inevitably require precisely manufactured prostheses in microscale or even nanoscale. It is anticipated that the MI-based technologies as well as MI-oriented technologies will be advanced in the near future.

TE can perhaps be best defined as the use of a combination of cells, engineering materials, and suitable biochemical factors to improve or replace biological functions in an effort to effect the advancement of medicine, indicating an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function for understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use. The term “regenerative medicine” is often used synonymously with “TE,” although those involved in regenerative medicine place more emphasis on the use of stem cells to produce tissues (<http://biomed.tamu.edu/bio-materials/TissueENgineering.htm>). TE *in vitro* and *in vivo* involves the interaction of cells with a material surface. The nature of the surface can directly influence cellular response, ultimately affecting the rate and quality of new tissue formation. Initial events at the surface include the orientated adsorption of molecules from the surrounding fluid, creating a conditioned interface to which the cell responds. The gross morphology as well as the microtopography and chemistry of the surface determine which molecules can adsorb and how cells will attach and align themselves. The local attachments made of the cells with their substrate determine cell shape, which, when transduced via the cytoskeleton to the nucleus, result in expression of specific phenotypes. Osteoblasts and chondrocytes are sensitive to subtle differences in surface roughness and surface chemistry. Boyan et al. [114] investigated the chondrocyte response to TiO_2 of differing crystallinities and showed that cells can discriminate between surfaces at this level as well. Cellular response also depends on the local environmental and state of maturation of the responding cells. It was mentioned that optimizing surface structure for site-specific TE is one option; modifying surfaces with biological ways is another biological engineering [114].

Scaffold material has a twofold function: as artificial extracellular matrices and as a spacer keeping a certain open space. Furthermore, scaffold material has to be dissolved completely into the living body after autocell is regenerated with artificial extracellular matrices [115]. There are several important biodegradable and/or biofunctional scaffold architectures, structures and materials. They include blended-polymer scaffolds, collagen-based scaffolds, and composite scaffolds of polyhydroxybutyrate–polyhydroxyvalerate with bioactive wollastonite (CaSiO_3) [116]. Using an ink-injection technique (<http://www.wipo/cgi-pct/guest/getbyKy5?Key=02>), a thin film (with thickness of about 0.1 mm) of calcium phosphate and binding agent is injected onto the substrate to build 3D bony-like structures [117]. Lee et al. [118] employed 3DP technology to fabricate porous scaffolds by inkjet printing liquid binder droplets. Direct 3DP, where the final scaffold materials are utilized during the actual 3DP process, imposes several limitations on the final scaffold structure. An indirect 3DP protocol was developed, where molds are printed and the final materials are cast into the mold cavity to overcome the limitations of the direct technique.

Results of SEM observations showed highly open, well interconnected, uniform pore architecture (about 100–150 μm) [118]. Scaffold materials for bone TE often are supplemented with bone morphogenetic proteins (BMPs). Walboomers et al. [119] investigated a bovine extracellular matrix product containing native BMPs. Hollow cylindrical implants were made from titanium fiber mesh and were implanted subcutaneously into the back of Wistar rats. It was reported that (i) after 8 weeks, in two out of six loaded specimens, newly formed bone and bone marrow-like tissues could be observed and (ii) after 12 weeks, this had increased to five out of six loaded samples. It was, therefore, concluded that the bovine extracellular matrix product loaded in a titanium fiber mesh tube showed bone-inducing properties [119].

Electrospinning [120] has recently emerged as a leading technique for generating biomimetic scaffolds made of synthetic and natural polymers for TE applications. Li et al. [121] compared collagen, gelatin (denatured collagen), solubilized α -elastin, and recombinant human tropoelastin as biopolymeric materials for fabricating tissue-engineered scaffolds by electrospinning. It was reported that (i) the average diameter of gelatin and collagen fibers could be scaled down to 200–500 nm without any beads, while the α -elastin and tropoelastin fibers were several microns in width and (ii) cell culture studies confirmed that the electrospun-engineered protein scaffolds support attachment and growth of human embryonic palatal mesenchymal cells [121]. For fabricating meshes of collagen and/or elastin by means of electrospinning from aqueous solutions, Buttafoco et al. [122] added polyethylene oxide and NaCl to spin continuous and homogeneous fibers. It was reported that (i) upon crosslinking, polyethylene oxide and NaCl were fully leached out and (ii) smooth muscle cells grew as a confluent layer on top of the crosslinked meshes after 14 days of culture.

Surface properties of scaffolds play an important role in cell adhesion and growth. Biodegradable poly(α -hydroxy acids) have been widely used as scaffolding materials for TE; however, the lack of functional groups is a limitation. Liu et al. [123] mentioned in their studies that gelatin was successfully immobilized onto the surface of poly(α -hydroxy acids) films and porous scaffolds by an entrapment process. It was found that (i) the amount of entrapped gelatin increased with the ratio of dioxane/water in the solvent mixture used, (ii) chemical crosslinking after physical entrapment considerably increased the amount of retained gelatin on the surface of poly(α -hydroxy acids), (iii) osteoblasts were cultured on these films and scaffolds, (iv) cell numbers on the surface-modified films and scaffolds were significantly higher than those on controls 4 h and 1 day after cell seeding, (v) the osteoblasts showed higher proliferation on surface-modified scaffolds than on the control during 4 weeks of *in vitro* cultivation, and (vi) more collagen fibers and other cell secretions were deposited on the surface-modified scaffolds than on the control scaffolds [123].

12.7 Hybridization and Multifunctionality

Biomaterials play a critical role in the success of TE approaches, as they guide the shape and structure of developing tissues, provide mechanical stability, and present

opportunities to deliver inductive molecules to transplanted or migrating cells. Therefore, the selection of the appropriate biomaterial can have a profound impact on the quality of newly formed tissue. A major challenge facing the field of TE is the development or identification of materials capable of promoting the desired cellular and tissue behavior. Given that few biomaterials possess all the necessary characteristics to perform ideally, engineers and clinicians alike have pursued the development of hybrid or composite biomaterials to synergize the beneficial properties of multiple materials into a superior matrix. The combination of natural and synthetic polymers with various other materials has demonstrated the ability to enhance cellular interaction, encourage integration into host tissue, and provide tunable material properties and degradation kinetics. The selection and utilization of numerous hybrid and composite materials to promote the formation of bone, vascular, and neural tissues should be crucial. It was mentioned that the continued development and implementation of hybrid biomaterials will lead to further successes in TE and regenerative medicine [124].

The ability to control hierarchical assemblies of hybrid nanostructures and biological building blocks is essential for a wide range of applications ranging from biomedical to sensing. One of the main challenges is to be able to control self-organization at a molecular level and thus provide control over the biological and inorganic interfaces under environmentally benign and biologically compatible conditions. Multifunctionality and improving the properties of materials make it necessary to use hybrid systems such as combinations of metals with polymers. Their applications can be found in all areas where lightweight, improved and adapted mechanical properties as well as high functionality are needed. Moreover, tailored types of hybrids can be interesting for biomedical applications, as under specific conditions they show, for example, good strength combined with high elasticity. Herein, we present preliminary tests on the biomimetic behavior of an AISI SS316L/polypropylene copolymer/AISI SS316L sandwich. Biomimetic coatings were produced by inducing a calcium phosphate layer in a way similar to the process of natural bone formation [125].

Tooth loss accompanied by alveolar bone resorption presents a significant clinical problem. The utility of a TE approach was investigated to provide corrective therapies for tooth-bone loss. Hybrid tooth-bone tissues were bioengineered as follows: tooth implants were generated from pig third molar tooth bud cells seeded onto polyglycolide (PGA) and polyglycolide-*co*-lactide (PLGA) scaffolds and grown for 4 weeks in the omenta of adult rat hosts. Bone implants were generated from osteoblasts induced from bone marrow progenitor cells obtained from the same pig, seeded onto PLGA fused wafer scaffolds, and grown for 10 days in a rotational oxygen-permeable bioreactor system. The tooth and bone implants were harvested, sutured together, reimplanted, and grown in the omenta for an additional 8 weeks. It was reported that (i) histological and immunohistochemical analyses of the excised hybrid tooth-bone constructs revealed the presence of tooth tissues, including primary and reparative dentin and enamel in the tooth portion of hybrid tooth-bone implants, and osteocalcin and bone sialoprotein-positive bone in the bone portion of hybrid tooth-bone constructs and (ii) collagen type III-positive

connective tissue resembling periodontal ligament and tooth root structures were present at the interface of bioengineered tooth and bone tissues, demonstrating that a hybrid tooth-bone TE approach can be employed for the eventual clinical treatment of tooth loss accompanied by alveolar bone resorption [126].

Over the past few decades, there has been great interest in the use of orthopedic and dental implants that integrate into tissue by promoting bone ingrowth or bone adhesion, thereby eliminating the need for cement fixation. However, strategies to create bioactive implant surfaces to direct cellular activity and mineralization leading to osseointegration are lacking. A preparation of a hybrid bone-implant material consisting of Ti-6Al-4V foam, whose 52% porosity is filled with a peptide amphiphile (PA) nanofiber matrix was reported [127]. These PA nanofibers can be highly bioactive by molecular design and are used here as a strategy to transform an inert titanium foam into a potentially bioactive implant. Using SEM and confocal microscopy, it was revealed that PA molecules self-assemble into a nanofiber matrix within the pores of the metallic foam, fully occupying the foam's interconnected porosity. Furthermore, the method allows the encapsulation of cells within the bioactive matrix, and under appropriate conditions the nanofibers can nucleate mineralization of calcium phosphate phases with a Ca:P ratio that corresponds to that of hydroxyapatite. Cell encapsulation was quantified using a DNA measuring assay and qualitatively verified by SEM and confocal microscopy. An *in vivo* experiment was performed using a bone plug model in the diaphysis of the hind femurs of a Sprague-Dawley rat and examined by histology to evaluate the performance of these hybrid systems after 4 weeks of implantation. Preliminary results demonstrate *de novo* bone formation around and inside the implant, vascularization around the implant as well as the absence of a cytotoxic response. It was concluded that the PA-Ti hybrid strategy could be potentially tailored to initiate mineralization and direct a cellular response from the host tissue into porous implants to form new bone and thereby improve fixation, osseointegration, and long-term stability of implants [127].

Orthopedic implant stability is not only a function of strength but also depends on the fixation established with surrounding tissues. A novel multiscaled hybrid orthopedic implant material consisting of a macroporous Ti scaffold was reported in Ref. [128]; the walls of such scaffolds have microporous titania layers which are fully covered with nanofibers of Sr-doped hydroxyapatite (Sr-HA), similar to that in Ref. [95]. The Sr-HA nanofibers grow hydrothermally on microporous titania that has been formed by microarc oxidation within and out of the macropores. Meanwhile, the hydrothermal formation of the Sr-HA nanofibers is also proposed. These nanofibers construct a network structure similar to the hierarchical organization of bone extracellular matrix, and the resulting nanofibrous surface displays superhydrophilicity and apatite-inducing ability. The nanofiber-walled scaffold favors enhanced cellular activity and osteoinduction and has a great potential for load-bearing orthotopic use even in unfavorable conditions such as patients with large bone defects or gaps as well as improving the fixation and long-term stability of implants. During the hydrothermal treatment, Sr-HA nanoprisms nucleate from $\text{Ca}_{0.5}\text{Sr}_{0.5}\text{TiO}_3$ preformed on the TiO_2 and grow in length to nanofibers at the

expense of Ca^{2+} , Sr^{2+} and PO_4^{3-} ions that migrate from the TiO_2 . These Sr-HA nanofibers construct a network structure similar to the hierarchical organization of bone extracellular matrix, and the resulting nanofibrous surface displays a firm adhesion to substrate, superhydrophilicity, and apatite-inducing ability. It was reported that (i) the induced apatite prefers to nucleate on the basal-faceted surfaces of Sr-HA nanofibers and (ii) the nanofiber-walled scaffold has a great potential for load-bearing orthotopic use [128].

Compared with titanium (Ti) and other metal implant materials, poly (ether—ether ketone) (PEEK) shows outstanding biomechanical properties. A number of studies have also reported attractive bioactivity for nano- TiO_2 (n- TiO_2). Nano- TiO_2 /PEEK nanocomposites were prepared, taking advantage of the unique properties of both PEEK polymer and n- TiO_2 . The *in vitro* and *in vivo* bioactivities of these nanocomposites were assessed against a PEEK polymer control. The effect of surface morphology or roughness on the bioactivity of the nano- TiO_2 /PEEK nanocomposites was also studied. Nano- TiO_2 /PEEK was successfully fabricated and cut into disks for physical and chemical characterization and *in vitro* studies and prepared as cylindrical implants for *in vivo* studies. Their presence on the surface and dispersion in the composites was observed and analyzed by SEM and transmission electron microscopy and X-ray photoelectron spectroscopy. Bioactivity evaluation of the nanocomposites revealed that pseudopods of osteoblasts preferred to anchor at areas where nano- TiO_2 was present on the surface. In a cell attachment test, smooth PEEK showed the lowest optical density value (0.56), while rough nano- TiO_2 /PEEK exhibited the highest optical density value (1.21). In *in vivo* studies, the percent bone volume value of nano- TiO_2 /PEEK was approximately twice as large as that of PEEK. It was also demonstrated that (i) nano- TiO_2 significantly improves the bioactivity of PEEK, especially if it has a rough composite surface and (ii) a nano- TiO_2 /PEEK composite with a rough surface could be a novel alternative implant material for orthopedic and dental applications [129].

12.8 Bioengineering and Biomaterial-Integrated Implant System

With the aforementioned supportive technologies, surfaces of dental and orthopedic implants have been remarkably advanced. These applications can include not only ordinal implant system but also miniaturized implants as well as customized implants. Dental implant therapy has been one of the most significant advances in dentistry in the past 25 years. The computer and medical worlds are both working hard to develop smaller and smaller components. Using a precise, controlled, MIS technique, the mini-dental implants (MDI) are placed into the jawbone. The heads of the implants protrude from the gum tissue and provide a strong, solid foundation for securing the dentures. It is a one-step procedure that involves MIS, no sutures, and none of the typical months of healing.

Advantages associated with the MDI are (1) it can provide immediate stabilization of a dental prosthetic appliance after a minimal invasive procedure. (2) It can be used in cases where traditional implants are impractical or when a different type of anchorage system is needed. (3) Healing time required for mini-implant placement is typically shorter than that associated with conventional two-stage implant placement and the accompanying aggressive surgical procedure. According to the clinical reports, a biometric analysis of 1029 mini-implants, 5 months to 8 years *in vivo*, showed that the MDI mini-implant system can be implemented for long-term prosthesis stabilization and delivers a consistent level of implant success [130].

In addition to the aforementioned miniature implants, an immediate loading as well as customized implants have been receiving attention recently. Conventionally, a dental implant patient is required to have two stages of treatment consisting of two dental appointments 5–6 months apart. Recently, a single-stage treatment has received attention. Placing an implant immediately or shortly after tooth extraction offers several advantages for the patient as well as for the clinician. These advantages include shorter treatment time, less bone sorption, fewer surgical sessions, easier definition of the implant position, and better opportunities for osseointegration because of the healing potential of the fresh extraction site [131–134]. Titanium bar (particularly the portions in direct contact to connective tissue and bony tissue) is machined to have the exact shape of the root portion of the extracted tooth of the patient. The expected outcome of this method is a perfect mechanical retention, and therefore an ideal osseointegration can be achieved. This is called a custom (or customized) implant, which is fabricated by the electro-discharge machining (EDM) technique. In addition to the immediate placement of dental implants, another concept has been introduced. Techniques such as stereoscopic lithography and computer-assisted design and manufacture (CAD/CAM) have been successfully used with computer-numerized control milling to manufacture customized titanium implants for single-stage reconstruction of the maxilla, hemimandible, and dentition without the use of a composite-made flap after tumors removal [135]. Nishimura et al. [136] applied this concept to dental implants to fabricate the individual and splinted customized abutments for all restoration of implants in partially edentulous patients. It was claimed that complicated clinical problems such as angulation, alignment, and position can be solved. However, with this technique, the periimplant soft tissues are allowed to heal 2–3 weeks so that at least two dental appointments are required.

Many oral implant companies have recently launched new products claiming unique, and sometimes bioactive, surfaces (about 150 companies are currently marketing 500 different dental implant systems; in 2000, only 20 companies were supplying 100 dental implant systems). The focus has shifted from surface roughness to surface chemistry and a combination of chemical manipulations on the porous structure. To properly explain the claims for new surfaces, it is essential to summarize current opinions on bone anchorage, with emphasis on the potential for biochemical bonding. There were two methods of implant anchorage or retention: mechanical and bioactive [137,138]. Mechanical retention basically refers to the metallic substrate systems such as titanium materials. The retention is based on

undercut forms such as vents, slots, dimples, screws, and so on, and involves direct contact between bone and implant with no chemical bonding. The osseointegration depends on biomechanical bonding. The potentially negative aspect of biomechanical bonding is that it is time consuming. Bioactive retention is achieved with bioactive materials such as HA or bioglass, which bond directly to bone, similar to the ankylosis of natural teeth. The bioactivity is the characteristic of an important material which allows it to form a bond with living tissues. It is important to understand that bioactive implants may, in addition to chemical bonding, show biomechanical anchorage; hence a given implant may be anchored through both mechanisms. Bone matrix is deposited on the HA layer because of some type of physiochemical interaction between bone collagen and the HA crystals of the implant [139].

Recent research has further redefined the retention means of dental implants into the terminology of osseointegration versus biointegration. When examining the interface at a higher magnification level, Sundgren et al. [140] showed that unimplanted Ti surfaces have a surface oxide (TiO_2) with a thickness of about 35 nm. During an implantation period of 8 years, the thickness of this layer was reported to increase by a factor of 10. Furthermore, calcium, phosphorous, and carbon were identified as components of the oxide layer, with the phosphorous strongly bound to oxygen, indicating the presence of phosphorous groups in the metal oxide layer. Many retrospective studies on retrieved implants as well as clinical reports confirm the aforementioned important evidence: (1) surface titanium oxide film grows during the implantation period and (2) calcium, phosphorous, carbon, hydroxyl ions, proteins, etc., are incorporated in an ever-growing surface oxide even inside the human biological environments [141,142]. Numerous *in vitro* studies on treated or untreated titanium surfaces were covered and to some extent were incorporated with Ca and P ions when such surfaces were immersed in SBF. Additionally, we know that bone and blood cells are rugophilia; hence, in order not only to accommodate for the bone growth but also to facilitate such cells' adhesion and spreading, titanium surfaces need to be textured to accomplish and show appropriate roughness. Furthermore, FG structure and design concept on materials and structures has been receiving special attention not only in industrial applications but also in dental and medical fields. Its importance becomes more clinically crucial when such structures and concepts are about to be applied to implants. For example, the majority of the implant mass should be strong and tough so that occlusal force can be smoothly transferred from the placed implant to the receiving hard tissue. However, the surface needs to be engineered to exhibit some extent of roughness. From such continuous changes in macrostructures from bulk core to the porous case, the structural integrity should be maintained. The FG can also be applied for the purpose of having continuous changes in a chemical (compositional) properties. Ca-, P-enrichment is not needed in the interior materials of the implants. Some other modifications related to chemical dressing or conditioning can also be utilized for achieving gradient functionality on chemical alternations on surfaces as well as near-surface zones.

Summarizing and ending this book, the author is proposing an ideal implant structure that is integrated by bioengineering and biomaterials science. Oshida previously proposed the four important factors and requirements for successful and

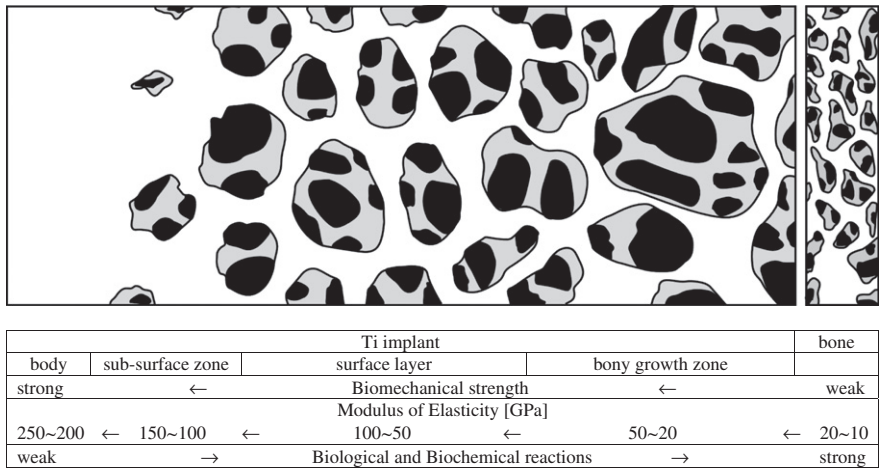


Figure 12.2 Schematic and conceptual Ti implant with gradient mechanical and biological functions.

biofunctional implant systems: biocompatibility, mechanocompatibility, macro- and micromorphological compatibility, and crystallographic (or nanomorphological) compatibility [143].

Figure 12.2 illustrates a schematic and conceptual Ti implant that possesses a gradual function of mechanical and biological behaviors so that mechanical and biological compatibility can be realized. Since microtextured Ti surfaces and/or porous Ti surfaces promote fibroblast apposition and bone ingrowth, the extreme left side representing the solid Ti implant body should have gradually increased internal porosities toward the right side, which is in contact with vital hard/soft tissue. Accordingly, mechanical strength of this implant system decreases gradually from left to right, whereas biological activity increases from left to right. Therefore, the mechanical compatibility can be completely achieved, and it can be easily understood by referring to Figure 6.1. Porosity-controlled surface zones can be fabricated by an electrochemical technique, polymeric sponge replication method, P/M technique, superplastic diffusion bonding method, or foamed metal structure technique.

Once the Ti implant is placed in hard tissue, TiO_2 grows and increases its thickness, due to more oxygen availability inside the body fluid as well as the coexistence of superoxidant. It is very important to mention here that Ti is not in contact with the biological environment, but rather there is a gradual transition from the bulk Ti material, stoichiometric oxide (i.e., TiO_2), hydrated polarized oxide, adsorbed lipoproteins and glycolipids, collagen filaments, and bundles of collagen filaments to cells. Such gradient functional structure was also fabricated in CpTi and microtextured polyethylene terephthalate systems. In addition, a gradient structural system of Ti and TiN was developed. During HA coating, a gradient functional layer was successfully fabricated. To promote these GF and graded structural transitions, there are many *in vivo* as well as *in vitro* evidences indicating that surface titanium oxide

is incorporated with mineral ions, water, and other constituents of biofluids. Since a surface layer of TiO_2 is negatively charged, the calcium ion attachment can be easily achieved. Retrieved Ti implants showed that surface TiO_2 was incorporated with Ca and P ions, while *in vitro* treatment of TiO_2 in extracellular fluids or SBF for prolonged periods of incubation time resulted in the incorporation of Ca, P, and S ions into TiO_2 . Without prolonged treatment, there are several methods proposed to conduct relatively short-time incubation for the incorporation of Ca and P ions. For example, TiO_2 can be electrochemically treated in an electrolyte of a mixture of calcium acetate monohydrate and calcium glycerophosphate. As a result of incorporation of Ca and P ions, bone-like hydroxyapatite can be formed in macroscale or nanodimension. Again for reducing the incubation time, bone-like hydroxyapatite crystals can be formed by treating the TiO_2 surface with water and hydrogen plasma immersion ion implantation, followed by immersion in SBF, or by treating in hydrogen peroxide followed by SBF immersion, or immersion in SBF while treating the TiO_2 surface with microarc oxidation and irradiation with UV light. It is also known that P ions can be incorporated into TiO_2 while it is immersed in the human serum.

Bony growth super-surface zones should have a same roughness as the roughness of receiving hard tissue through microporous texturing techniques. This area can be structured using nanotube concepts. Because this zone responds strongly to osseointegration, the structure as well as the chemistry should accommodate favorable osteoinductive reactions. Both BMP and nanoapatite can be coated. The zone may be treated by femtosecond laser machining to build a microscale 3D scaffold which is structured inside the macroporosities. Such a scaffold can be made of biodegradable material (e.g., chitosan), which is incorporated with protein, Ca, P, apatite particles, or other species possessing bone growth factors.

References

- [1] Hench LL. Biomaterials: a forecast for the future. *Biomaterials* 1998;19:1419–23.
- [2] Utsunomiya S, Wang LM, Yudintsev S, Ewing RC. Ion irradiation-induced amorphization and nano-crystal formation in garnets. *J Nucl Mater* 2002;303:177–87.
- [3] Sakuntala T, Arora AK, Sivasubramanian V, Rao R, Kalavathy S, Deb SK. Pressure induced amorphization and decomposition in ZrV_2O_7 : a Raman spectroscopic study. *Phys Rev* 2007;B75:1–6.
- [4] Korotaev AD, Tyumentsev AN. Amorphization of metals by ion implantation and ion mixing methods. *Russ Phys J* 1994;37:703–24.
- [5] Inoue A. Recent progress of Zr-based bulk amorphous alloys. *Sci Rep RITU* A42;1996:1–11.
- [6] Tregilgas J. Amorphous hinge material. *Adv Mater Process* 2005;163:46–9.
- [7] Inoue A. Synthesis and properties of Ti-based bulk amorphous alloys with a large supercooled liquid region. *Mater Sci Forum* 1999;313/314:307–14.
- [8] Louzguine DV, Inoue A. Multicomponent metastable phase formed by crystallization of Ti–Ni–Cu–Sn–Zr amorphous alloy. *J Mater Res* 1999;14:4426–30.
- [9] Zhang T, Inoue K. Preparation of Ti–Cu–Ni–Si–B amorphous alloy with a large supercooled liquid region. *Mater Trans JIM* 1999;40:301–6.

- [10] Masumoto T. Amorphous Ti–Cu system alloys. Japan Patent Application Laid-Open No.7-54086; 1995.
- [11] Tsuji N. Accumulative roll bonding. <http://onlinelibrary.wiley.com/doi/10.1002/adem.200310077/pdf>.
- [12] Karlík M, Homola P, Slámová M. Accumulative roll-bonding: first experience with a twin-roll cast AA8006 alloy. *J Alloys Compd* 2004;378:322–5.
- [13] Tsuji N, Saito Y, Lee SH, Minamino YARB. (Accumulative roll-bonding) and other new techniques to produce bulk ultrafine grained materials. *Adv Eng Mater* 2003;5:338–44.
- [14] Raducanu D, Vasilescu E, Cojocaru VD, Cinca I, Drob P, Vasilescu C, et al. Mechanical and corrosion resistance of a new nanostructured Ti–Zr–Ta–Nb alloy. *J Mech Behav Biomed Mater* 2011;4:1421–30.
- [15] Kishi Y. 3D structure of metallic fibers with high porosity. Japan Patent Application Laid-Open No. P07A012851; 2006.
- [16] Shen M, Bever J. Gradients in polymeric materials. *Mater Sci* 1972;7:741–6.
- [17] Mortensen A, Suresh S. Functionally graded metals and metal–ceramic composites. Part 1. *Process Int Mater Rev* 1995;40:239–65.
- [18] Kieback B, Neubrand A, Riedel H. Processing techniques for functionally graded materials. *Mater Sci Eng* 2003;A362:81–105.
- [19] JETRO. Ti–O coating on Ti–6Al–4V alloy by DC reactive sputtering method. *New Technol Jan* 1994;22:18 No. 94-06-001-01
- [20] Bogdanski D, Köller M, Müller D, Muhr G, Bram M, Buchkremer HP, et al. Easy assessment of the biocompatibility of Ni–Ti alloy by in vitro cell culture experiments on a functionally graded Ni–NiTi–Ti material. *Biomaterials* 2002;23:4549–55.
- [21] Hedia HS. Effect of cancellous bone on the functionally graded dental implant concept. *Biomed Mater Eng* 2005;15:199–209.
- [22] Wang F, Lee HP, Lu C. Thermal–mechanical study of functionally graded dental implants with the finite element method. *J Biomed Mater Res A* 2007;80:146–58.
- [23] Traini T, Mangano C, Sammons RL, Mangano F, Macchi A, Piattelli A. Direct laser metal sintering as a new approach to fabrication of an isoelastic functionally graded material for manufacturing of porous titanium dental implants. *Dent Mater* 2008;24:1525–33.
- [24] Petzold C, Rubert M, Lyngstadaas SP, Ellingsen JE, Monjo M. *In vivo* performance of titanium implants functionalized with eicosapentaenoic acid and UV irradiation. *J Biomed Mater Res Part A* 2010;96:83–92.
- [25] Pompe W, Worch H, Eppler M, Friess W, Gelinsky M, Greil P, et al. Functionally graded materials for biomedical applications. *Mater Sci Eng* 2003;A362:40–60.
- [26] Leong KF, Chua CK, Sudarmadji N, Yoeng WY. Engineering functionally graded tissue engineering scaffolds. *J Mech Behav Biomed Mater* 2008;2:140–52.
- [27] Lewis NASA. Research center. Sputter texturing to produce surfaces for bonding. NASA Tech Briefs 1997;May:81 www.nasatech.com
- [28] Banks BA. Improved texturing of surgical implants for soft tissues. LEW-15805. NASA Tech Briefs 1997;21:70.
- [29] Fujibayashi S, Neo M, Kim H-M, Kokubo K, Nakamura T. Osteoinduction of porous bioactive titanium metal. *Biomaterials* 2004;25:443–50.
- [30] Asaoka K, Kuwayama N, Okuno O, Miura I. Mechanical properties and biomechanical compatibility of porous titanium for dental implants. *J Biomed Mater Res* 1985;19:699–713.

- [31] Heinel P, Müller L, Körner C, Singer RF, Müller FA. Cellular Ti–6Al–4V structures with interconnected macro porosity for bone implants fabricated by selective electron beam melting. *Acta Biomater* 2008;4:1536–44.
- [32] Li Y, Xiong J, Wong CS, Hodgson PD, Wen C. Ti6Ta4Sn alloy and subsequent scaffolding for bone tissue engineering. *Tissue Eng Part A* 2009;15:3151–9.
- [33] Park JW, Kim YJ, Jang JH, Song H. Osteoblast response to magnesium ion-incorporated nanoporous titanium oxide surfaces. *Clin Oral Implants Res* 2010;21:1278–87.
- [34] Yamada M, Ueno T, Minamikawa H, Ikeda T, Nakagawa K, Ogawa T. Early-stage osseointegration capability of a submicrofeatured titanium surface created by micro-roughening and anodic oxidation. *Clin Oral Implants Res* 2012;June [Abstract only].
- [35] Wheeler KR, Karagianes MT, Sump KR. Porous titanium alloy for prosthesis attachment. Titanium alloys in surgical implants. Phoenix, AZ: ASTM Proc.; 1983. p. 241–54.
- [36] Engelhard G, Zaharias R, Keller JC. Effects of CP Ti surface roughness on osteoblast mineralization. *J Dent Res* 1995;74:189 [Abstract No. 1424]
- [37] Petronis S, Gretzer C, Kasemo B, Gold J. Model porous surfaces for systematic studies of material–cell interactions. *J Biomed Mater Res* 2003;66A:707–21.
- [38] Xiaoxiong M, Shizhong H. The states of bromide on titanium surface prior to pit initiation. *J Chin Soc Corr Protect* 1989;9:29–35.
- [39] Ungersboeck A, Pohler OEM, Perren SM. Evaluation of soft tissue reactions at the interface of titanium limited contact dynamic compression plate implants with different surface treatments: an experimental sheep study. *Biomaterials* 1996;17:797–806.
- [40] Larsson C, Thomsen P, Aronsson BO, Rodahl M, Lausmaa J, Kasemo B, et al. Bone response to surface-modified titanium implants: studies on the early tissue response to machined and electropolished implants with different oxide thickness. *Biomaterials* 1996;17:605–16.
- [41] Chung FH, McAlarney ME. Effects of variations in surface treatment on titanium topography. *J Dent Res* 1995;74:112 [Abstract No. 802].
- [42] Thelen S, Barthelat F, Brinson LC. Mechanics considerations for microporous titanium as an orthopedic implant material. *J Biomed Mater Res* 2004;69A:601–10.
- [43] Oshida Y. Requirements for successful, biofunctional implants. In: Yahia L'H, editor. *Proceedings of the 1st International Symposium on Advanced Biomaterials (SIBA)*. Montréal: Ecole Polytechnique. 2000, p. 5.
- [44] Takemoto M, Fujibayashi S, Neo M, Suzuki J, Kokubo T, Nakamura T. Mechanical properties and osteoconductivity of porous bioactive titanium. *Biomaterials* 2005;26:6014–23.
- [45] Kohn DH, Ducheyne P. A parametric study of the factors affecting the fatigue strength of porous coated Ti–6Al–4V implant alloy. *J Biomed Mater Res* 1990;24:1483–501.
- [46] Zou C, Zhang E, Li M, Zeng S. Preparation, microstructure and mechanical properties of porous titanium sintered by Ti fibres. *J Mater Sci Med* 2008;19:401–5.
- [47] Li X, Wng CT, Zhang WG, Li YC. Properties of a porous Ti–6Al–4V implant with a low stiffness for biomedical application. *Proc Inst Mech Eng H* 2009;223(2):173–8.
- [48] Espana F, Balla VK, Bose S, Ohgami Y, Davies NM, Bandyopadhyay A. Influence of porosity on mechanical properties and in vivo response of Ti6Al4V implants. *Acta Biomater* 2010;6:1640–8.
- [49] Energy Research & Generation, Inc. Duocel foam metal: a new basic design material; 1998.

- [50] Topin F, Bonnet JP, Madani B, Tadrist L. Experimental analysis of multiphase flow in metallic foam: flow laws, heat transfer and convective boiling. *Adv Eng Mater* 2006;8:890–9.
- [51] Banhart J. Manufacture, characterization and application of cellular metals and metal foams. *Prog Mater Sci* 2001;46:559–632.
- [52] DeGroot CT, Straatman AG, Betchen LJ. Modeling forced convection in finned metal foam heat sinks. *J Electron Packag* 2009;131:021001. doi:10.1115/1.3103934.
- [53] Banhart J. Manufacturing routes for metallic foams. *J Met* 2000;52:22–7 <<http://www.tms.org/pubs/journals/JOM/0012/Banhart-0012.html/>>. Retrieved 2012-01-20
- [54] Oshida Y, Hashem A, Nishihara T, Yapchulay MV. Fractal dimension analysis of mandibular bones: towards a morphological compatibility of implants. *J Biomed Mater Eng* 1994;4:397–407.
- [55] Page L. Fraunhofer boffins develop ‘Titanium foam’ endoskeletal implants. <http://www.theregister.co.uk/2010/09/24/titanium_foam/>
- [56] Singh R, Lee PD, Lindley TC, Dashwood RJ, Ferrie E, Imwinkelried T. Characterization of the structure and permeability of titanium foams for spinal fusion devices. *Acta Biomater* 2009;5:477–87.
- [57] Singh R, Lee PD, Jones JR, Poologasundarampillai G, Post T, Lindley TC, et al. Hierarchically structured titanium foams for tissue scaffold applications. *Acta Biomater* 2010;6:4596–604.
- [58] Agarwal A, McKechnie T, Sudipta S. Net shape nanostructured aluminum oxide structures fabricated by plasma spray forming. *J Therm Spray Technol* 2003;12:350–9.
- [59] Ou H, Wand P, Lu B, Long H. Finite element modeling and optimisation of net-shape metal forming processes with uncertainties. *Comput Struct* 2012;90/91:13–27.
- [60] Jazi HS. Near-net shape forming of Ti–6Al–4V by vacuum plasma spraying under construction. <<http://www.mie.utoronto.ca/labs/cact/Research/VPSF/VPSF.html/>>
- [61] Cominotti R, Gentili E. Near net shape technology: an innovative opportunity for the automotive industry. *Robot Comput Integr Manuf* 2008;24:722–7.
- [62] Ringeisen BR, Chrisey DB, Piqué A, Krizman D, Bronks M, Spargo B. Direct write technology and a tool to rapidly prototype patterns of biological and electronic systems. *Nanotech* 2001;1:414–7.
- [63] Finke S, Feenstra K. Solid freedom fabrication by extrusion and deposition of semi-solid alloys. *J Mater Sci* 2002;37:3101–6.
- [64] Klug KL, Ucock I, Gungor MN, Gulu M, Kramer LS, Tack WT, et al. The near-net-shape manufacturing of affordable titanium components for the M777 lightweight howitzer. *J Met* 2004;56:35–42.
- [65] Baier RE. Conditioning surfaces to suit the biomedical environment: Recent Progress. *J Biomech Eng* 1982;104:257–71.
- [66] Domanski M, Winnubst L, Luttge R, Lamers E, Walboomers XF, Jansen J, et al. Production and characterization of micro- and nano-features in biomedical alumina and zirconia ceramics using a tape casting route. *J Mater Sci Mater Med* 2012;23:1637–44.
- [67] Best SM, Porter AE, Thian ES, Huang J. Bioceramics: past, present and for the future. *J Eur Ceram Soc* 2008;28:1319–27.
- [68] Larry LH. Bioceramics: from concept to clinic. *J Am Ceram Soc* 1991;74:1487–510.
- [69] Eisenbarth E, Meyle J, Nachtigall W, Breme J. Influence of the surface structure of titanium materials on the adhesion of fibroblasts. *Biomaterials* 1996;17:1399–403.

- [70] Heydarkhan-Hagvall S, Choi CH, Dunn J, Heydarkhan S, Schenke-Layland K, MacLellan WR, et al. Influence of systematically varied nano-scale topography on cell morphology and adhesion. *Cell Commun Adhes* 2007;14:181–94.
- [71] Parker JA, Walboomers XF, Von den Hoff JW, Maltha JC, Jansen JA. The effect of bone anchoring and micro-grooves on the soft tissue reaction to implants. *Biomaterials* 2002;23:3887–96.
- [72] Pfeiffer F, Herzog B, Kern D, Scheideler L, Geis-Gerstorfer J, Wolburg H. Cell reactions to microstructured implant surfaces. *Microelectron Eng* 2003;67/68:913–22.
- [73] Balasundaram G, Sato M, Webster J. Using hydroxyapatite nanoparticles and decreased crystallinity to promote osteoblast adhesion similar to functionalizing with RGD. *Biomaterials* 2006;27:2798–805.
- [74] Treccani L, Maiwald M, Zöllmer V, Busse M, Grathwol G, Rezwan K. Antibacterial and abrasion-resistant alumina micropatterns. *Adv Eng Mater* 2009;11:B61–6.
- [75] Tomsia AP, Launey ME, Lee JS, Mankani MH, Wegst UGK, Saiz E. Nanotechnology approaches to improve dental implants. *Int J Oral Maxillofac Implants* 2011; 26(suppl):25–44.
- [76] Tsukimura N, Ueno T, Iwasa F, Minamikawa H, Sugita Y, Ishizaki K, et al. Bone integration capability of alkali- and heat-treated nanobiomimetic Ti–15Mo–5Zr–3Al. *Acta Biomater* 2011;7:4267–77.
- [77] Chen F, Lam WM, Lin CJ, Qiu GX, Wu ZH, Luk KD, et al. Biocompatibility of electrophoretic deposition of nanostructured hydroxyapatite coating on roughen titanium surface; in vitro evaluation using mesenchymal stem cells. *J Biomed Mater Res B Appl Biomater* 2007;82:183–91.
- [78] Li Y, Lee IS, Cui FZ, Choi SH. The biocompatibility of nanostructural calcium phosphate coated on micro-arc oxidized titanium. *Biomaterials* 2008;29:2025–32.
- [79] He F, Yang G, Wang X, Zhao S. Effect of electrochemically deposited nanohydroxyapatite on bone-bonding of sandblasted/dual acid-etched titanium implants. *Int J Oral Maxillofac Implants* 2009;24:790–9.
- [80] Lin A, Wang CJ, Kelly J, Gubbi P, Nihimura I. The role of titanium implant surface modification with hydroxyapatite nanoparticles in progressive early bone–implant fixation in vivo. *Int J Oral Maxillofac Implants* 2009;24:808–16.
- [81] Park JW, Kim HK, Kim YJ, An CH, Hanawa T. Enhanced osteoconductivity of microstructured titanium implants (XiVE S CELLplus™) by addition of surface calcium chemistry: a histomorphometric study in the rabbit femur. *Clin Oral Implants Res* 2009;20:684–90.
- [82] Lee K, Ko YM, Choe HC, Kim BH. Formation of nano-phase hydroxyapatite film on TiO₂ nano-network. *J Nanosci Nanotechnol* 2012;12:822–7.
- [83] Nicula R, Lüthen F, Stir M, Niebe B, Burkel E. Spark plasma sintering synthesis of porous nanocrystalline titanium alloys for biomedical applications. *Biomol Eng* 2007;24:564–7.
- [84] Ercan B, Taylor E, Alpaslan E, Webster TJ. Diameter of titanium nanotubes influences anti-bacterial efficacy. 2011 Nanotech 2011;22:295102.
- [85] Puckett SD, Lee PP, Ciombor DM, Aaron RK, Webster TJ. Nanotextured titanium surfaces for enhancing skin growth on transcutaneous osseointegrated devices. *Acta Biomater* 2010;6:2352–62.
- [86] Balasundaram G, Yao C, Webster TJ. TiO₂ nanotubes functionalized with regions of bone morphogenetic protein-2 increases osteoblast adhesion. *J Biomed Mater Res A* 2008;84:447–53.
- [87] Ogawa T, Saruwatari L, Takeuchi K, Aita H, Ohno N. Ti nano-nodular structuring for bone integration and regeneration. *J Dent Res* 2008;87:751–6.

- [88] Sjöström T, Dalby MJ, Hart A, Tare R, Oreffo RO, Su B. Fabrication of pillar-like titania nanostructures on titanium and their interactions with human skeletal stem cells. *Acta Biomater* 2009;5:1433–41.
- [89] Puckett SD, Taylor E, Raimondo T, Webster TJ. The relationship between the nanostructure of titanium surfaces and bacterial attachment. *Biomaterials* 2010;31:706–13.
- [90] Bae IH, Yun KD, Kim HS, Jeong BC, Lim HP, Park SW, et al. Anodic oxidized nanotubular titanium implants enhance bone morphogenetic protein-2 delivery. *J Biomed Mater Res B Appl Biomater* 2010;93:484–91.
- [91] Yu WQ, Qui J, Zhang FQ. In vitro corrosion study of different TiO₂ nanotube layers on titanium in solution with serum proteins. *Colloids Surf Biointerf* 2011;84:400–5.
- [92] Cui CX, Gao X, Qi YM, Liu SJ, Sun JB. Microstructure and antibacterial property of in situ TiO(2) nanotube layer/titanium biocomposites. *J Mech Behav Biomed Mater* 2012;5:178–83.
- [93] Feng XJ, Macak JM, Albu SP, Schmuki P. Electrochemical formation of self-organized anodic nanotube coating on Ti–28Zr–8Nb biomedical alloy surface. *Acta Biomater* 2008;4:318–23.
- [94] Sul YT. Electrochemical growth behavior, surface properties, and enhanced in vivo bone response of TiO₂ nanotubes on microstructured surfaces of blasted, screw-shaped titanium implants. *Int J Nanomed* 2010;87:87–100.
- [95] Xin Y, Jiang J, Huo K, Hu T, Chu PK. Bioactive SrTiO(3) nanotube arrays: strontium delivery platform on Ti-based osteoporotic bone implants. *ACS Nano* 2009;3:3228–34.
- [96] Yu WQ, Qiu J, Xu L, Zhang FQ. Corrosion behaviors of TiO₂ nanotube layers on titanium in Hank's solution. *Biomed Mater* 2009;4:5012–8.
- [97] Sjöström T, Fox N, Su B. Through-mask anodization of titania dot- and pillar-like nanostructures on bulk Ti substrates using a nanoporous anodic alumina mask. *Nanotech* 2009;20:305–12.
- [98] Chiang CY, Chiou SH, Yang WE, Hsu ML, Yung MC, Tsai ML, et al. Formation of TiO₂ nano-network on titanium surface increases the human cell growth. *Dent Mater* 2009;25:1022–9.
- [99] Brammer KS, Oh S, Frandsen CJ, Jin S. TiO₂ nanotube structures for enhanced cell and biological functionality. *J Met* 2010;62:50–5.
- [100] Hori N, Iwasa F, Ueno T, Takeuchi K, Tsukimura N, Yamada M, et al. Selective cell affinity of biomimetic micro–nano-hybrid structured TiO₂ overcomes the biological dilemma of osteoblasts. *Dent Mater* 2010;26:275–87.
- [101] Macak JM, Tsuchiya H, Taveira L, Ghicov A, Schmuki P. Self-organized nanotubular oxide layers on Ti–6Al–7Nb and Ti–6Al–4V formed by anodization in NH₄F solutions. *J Biomed Mater Res* 2005;75A:928–33.
- [102] Oh SH, Finõnes RR, Daraio C, Chen LH, Jin S. Growth of nano-scale hydroxyapatite using chemically treated titanium oxide nanotubes. *Biomaterials* 2005;26:4938–43.
- [103] Goto K, Tamura J, Shinzato S, Fujibayashi S, Hashimoto M, Kawashita M, et al. Bioactive bone cements containing nano-sized titania particles for use as bone substitutes. *Biomaterials* 2005;26:6496–505.
- [104] Sato M, Sambito MA, Aslani A, Kalkhoran NM, Slamovich EB, Webster TJ. Increased osteoblast functions on undoped and yttrium-doped nanocrystalline hydroxyapatite coatings on titanium. *Biomaterials* 2006;27:2358–69.
- [105] Kim EJ, Kim WG, Jeong YH, Choe HC. Nanotubular oxide surface and layer formed on the Ti–35Ta–xZr alloys for biomaterials. *J Nanosci Nanotech* 2011;11:7433–7.

- [106] Divya Rani VV, Manzoor K, Menon D, Selvamurugan N, Nair SV. The design of novel nanostructures on titanium by solution chemistry for an improved osteoblast response. *Nanotech* 2009;20:195101.
- [107] MacDonald RA, Laurenzi BF, Viswanathan G, Ajayan PM, Stegmann JP. Collagen-carbon nanotube composite materials as scaffolds in tissue engineering. *J Biomed Mater Res* 2005;74A:489–96.
- [108] Funakoshi T, Majima T, Iwasaki N, Yamane S, Masuko T, Minami A, et al. Novel chitosan-based hyaluronan hybrid polymer fibers as a scaffold in ligament tissue engineering. *J Biomed Mater Res* 2005;74A:338–46.
- [109] Ni S, Chang J, Chou L. A novel bioactive porous CaSiO_3 scaffold for bone tissue engineering. *J Biomed Mater Res* 2006;76A:196–205.
- [110] Wu L, Jing D, Ding JA. “Room-temperature” injection molding/particulate leaching approach for fabrication of biodegradable three-dimensional porous scaffolds. *Biomaterials* 2006;27:185–91.
- [111] Taylor J. Nanobiotechnology. <<http://www.dti.gov.uk/>>.
- [112] Tyas MJ. Minimum intervention dentistry—the cutting edge? <<http://www.mdhs.unimelb.edu.au/>>.
- [113] Minimally invasive surgery. <<http://www.wpahs.org/agh/mis/>>.
- [114] Boyan BD, Hummert TW, Dean DD, Schwartz Z. Role of materials surfaces in regulating bone and cartilage cell response. *Biomaterials* 1996;17:137–46.
- [115] Taira M, Araki Y. Scaffolds for tissue engineering—kinds and clinical application. *J Dent Eng* 2005;152:27–30.
- [116] Li H, Chang J. Fabrication and characterization of bioactive wollastonite/PHBV composite scaffolds. *Biomaterials* 2004;25:5473–80.
- [117] Burgess DS. InkJet technique precludes microvessels and microlenses. *Technol World* 2005;May:213.
- [118] Lee M, Dunn JCY, Wu BM. Scaffold fabrication by indirect three-dimensional printing. *Biomaterials* 2005;26:4281–9.
- [119] Walboomers XF, Jansen JA. Bone tissue induction, using a COLLOSS[®]-filled titanium fibre mesh-scaffolding material. *Biomaterials* 2005;26:4779–85.
- [120] Hohman MM, Shin M, Rutledge G, Brenner MP. Electrospinning and electrically forced jets. *Phys Fluids* 2001;13:2201–20.
- [121] Li M, Mondrinos MJ, Gandhi MR, Ko FK, Weiss AS, Lelkes PI. Electropun protein fibers as matrices for tissue engineering. *Biomaterials* 2005;26:5999–6008.
- [122] Buttafoco L, Kolkman NG, Engbers-Buijtenhuijs P, Poot AA, Dijkstra PJ, Vermes I, et al. Electrospinning of collagen and elastin for tissue engineering applications. *Biomaterials* 2006;27:724–34.
- [123] Liu X, Won Y, Ma PX. Surface modification of interconnected porous scaffolds. *J Biomed Mater Res* 2005;74A:84–91.
- [124] Davis HE, Leach JK. Chapter 10: hybrid and composite biomaterials. In: Ashammakh A, editor. *Tissue Engineering*; 2008. p. 1–26. <http://www.oulu.fi/spareparts/ebook_to-pics_multifunctional/abstracts/davis.pdf/>
- [125] Palkowski H, Stanic V, Carradò A. Multilayer roll-bonded sandwich: processing, mechanical performance, and bioactive behavior. *J Met* 2012;64:514–9.
- [126] Young CS, Abukawa H, Asrican R, Ravens M, Troulis MJ, Kaban LB, et al. Tissue-engineered hybrid tooth and bone. *Tissue Eng* 2005;11:1599–610.
- [127] Sargeant TD, Guler MO, Oppenheimer SM, Mata A, Satcher RL, Dunand DC, et al. Hybrid bone implants: self-assembly of peptide amphiphile nanofibers within porous titanium. *Biomaterials* 2008;29:161–71.

- [128] Han Y, Zhou J, Zhang L, Xu K. A multi-scaled hybrid orthopedic implant: bone ECM-shaped Sr-HA nanofibers on the microporous walls of a macroporous titanium scaffold. *Nanotech* 2011;22:275–84.
- [129] Wu X, Liu X, Wei J, Ma J, Deng F, Wei S. Nano-TiO₂/PEEK bioactive composite as a bone substitute material: in vitro and in vivo studies. *Int J Nanomed* 2012;7:1215–25.
- [130] Bulard RA, Vance JB. Multi-clinic evaluation using mini-dental implants for long-term denture stabilization: a preliminary biometric evaluation. *Compend Condin Educ Dent* 2005;26:892–7.
- [131] Lazzarra RJ. Immediate implant placement into extraction sites: surgical and restorative advantages. *Int J Periodont Restor Dent* 1989;9:333–43.
- [132] Parel SK, Triplett RG. Immediate fixture placement: a treatment planning alternative. *Int J Oral Maxillofac Implants* 1990;5:337–45.
- [133] Werbitt MJ, Goldberg PV. The immediate implant. Bone preservation and bone regeneration. *Int J Periodont Restor Dent* 1992;12:207–17.
- [134] Gruder U, Polizzi G, Goebe R, Hatano N, Henry P, Jackson WJ, et al. 3-year prospective multicenter follow-up report on the immediate and delayed-immediate placement of implants. *Int J Oral Maxillofac Implants* 1999;14:210–6.
- [135] Peckitt NS. Stereoscopic lithography: customized titanium implants on orofacial reconstruction. *Br J Oral Maxillofac Surg* 1999;37:353–69.
- [136] Nishimura RD, Chang TL, Perri GR, Beumer J. Restoration of partially edentulous patients using customized implant abutments. *Pract Period Aesthet Dent* 1999;11:669–76.
- [137] De Putter M, de Lange GL, de Groot K. Permucosla dental implants of dense hydroxyapatite: fixation in alveolar bone May 1985, Brussels. Current Practice Series #29 Proceedings of the International congress on tissue integration in oral and maxillofacial reconstruction. Amsterdam: Excerta Media; 1986. p. 389–94
- [138] Albrektsson T, Wennerberg A. Oral implant surfaces: part 1—review focusing on topographic and chemical properties of different surfaces and in vitro responses to them. *Int J Prosthodont* 2004;17:536–43.
- [139] Denissen HW, Veldhuis AAH, van den Hooff A. Hydroxyapatite titanium implants May 1985, Brussels. Current Practice Series #29 Proceedings of the international congress on tissue integration in oral and maxillofacial reconstruction. Amsterdam: Excerta Media; 1986. p. 395–99
- [140] Sundgren JE, Bodo P, Lundström I. Auger electron spectroscopic studies of the interface between human tissue and implants of titanium and stainless steel. *J Colloid Interf Sci* 1986;11:9–20.
- [141] Albrektsson T, Wennerberg A. Oral implant surfaces: part 1—review focusing on topographic and chemical properties of different surfaces and in vivo responses to them. *Intl J Prosthodont* 2004;17:536–43.
- [142] Ellingsen JE. A study on the mechanism of protein adsorption to TiO₂. *Biomaterials* 1991;12:593–6.
- [143] Oshida Y. Requirements for successful biofunctional implants. In: Yahia L'H, editor. Proceedings of the international second symposium on advanced biomaterials. Montreal Canada; 2000. p. 5.

This page intentionally left blank

Epilogue

It is said that about 2 million journals are published annually, in which about 20,000 journals contain articles related, to some extent, to the biomedical area. Furthermore, out of 20,000 journals, about 500 journals have at least one article related to medicine and/or dentistry. Hence, we have to look over 500 journals to cover, at least superficially, the medical/dental articles. Suppose that we spend 1 h every day reading through such journals, and 15 min for each journal; we would need 125 days to cover all possible articles that might be useful to our expertise to avoid the delay for updated follow-up. Obviously, what this calculation indicates is that we need to spend at least one out of every three days going through all the journals. Today, journals such as *Biomaterials*, *Biomedical Materials Research*, *Journal of Dental Research*, *Dental Materials Research*, *Materials Science: Materials in Medicine*, *Biomedical Materials and Engineering*, *Mechanical Behavior of Biomaterials*, *Prosthetic Dentistry*, *Oral Maxillofacial Implants*, *Tissue Engineering*, *Nanotechnology*, and so on and so forth have at least three articles in each issue that are related to titanium materials.

I have also found while writing this book that most European journals contain few references cited from American journals or American authors, and vice versa. In addition to this unique phenomenon, there are quite a few excellent works done by Asian researchers published in obscure journals. I paid special attention to equalizing this imbalance by referring to the many excellent articles written by internationally recognized researchers.

My experience writing this book was similar to that of a painter who must decide when and how to finish his work. I knew that every month I would have to stop and read about 20 good articles before I would be able to finish this book. I did not want to miss any crucial articles, and at the same time, I have a fear that I might miss some because I had to stop reading journal articles to analyze them up to the June issue of the year 2006 for the first edition and for this second edition I included publications from July 2006 to August issue of the year 2012. As we are well aware, several journals offer an open-publication system, so that readers have a wonderful opportunity to access updated results and valuable information on time. This benefit should also be extended to researchers for their quick submission and publication, so that researchers can have direct/indirect communication almost on time basis.

As the population of the elderly increases, special care and attention should be paid to managing the diseases and pains specific to this population. For example, a geriatric dentist needs to be seriously changed to accommodate such social changes and challenges. Orthopedic and dental implants still have a window left to be further developed to facilitate the aged society, since implant receiving vital hard

tissue is gradually deteriorating (in sense of reducing bone density and quality). But I have a great hope that, during analyzing numerous articles, since the research and development in this sector has been so advanced and well developed, sooner or later public health services will become much easier and cheaper for coming years.

Closing this small book, I admit to having a very long list of individuals' names to be mentioned including those of teachers who inspired me, friends and colleagues who challenged me, and, most importantly, students (some of whom are now my colleagues) who continue to both inspire and challenge me. To all of them, I owe my knowledge and capability to comprehend the cited articles presented in this book. These people, who were and are valuable to me and to this book, should at least include the late T. Nakayama, S. Iguchi, V. Weiss, H.W. Liu, the late J.A. Schwartz, T. Koizumi, Y. Miwa, N. Saotome, T. Nishihara, F. Farzin-Nia, R. Sachdeva, S. Miyazaki, P.-C. Chen, M. Okamura, G.K. Stookey, C.J. Andres, T.M. Barco, M. Kowolik, D. Burr, M. Siefert, J.A. Parr, R. Miyamoto, F. Barbosa, V. John, J. Williams, O. Okuno, A. Zuccari, A. Hashem, A. Wu, M. Yapchulay, S. Isikbay, C. Kuphasuk, C-M. Lin, I. Garcia, W. Panyayong, Y.-J. Lim, M. Reyes, W.C. Lim, J.-C. Chang, S. Al-Ali, B. Anbari, D. Bartovic, F. Hernandez, I.W. Koh, Z.H. Khabbaz, R. Xirouchaki, P. Agarwal, N. Al-Nasr, C.B. Sellers, J. Dunigan-Miler, S. Al-Johancy, C.S. Wang, E. Matsis, R. Rani, Y.-C. Wu, K. Mirza, I. Katsilieri, C.N. Elias, E.B. Tuna, O. Aktören, K. Gençay, JIP (Japan Implant Practice) members and L.A. Oshida. Special thanks should also go to M.A. Dirlam for his excellent professional illustrations of all figures in this book, and J.D. Kummer for painstakingly proofreading the text. Thank you all.